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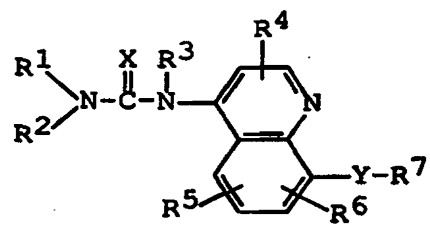
(54) Title: QUINOLINE DERIVATIVES AS H^+–ATPase INHIBITORS AND AS BONE RESORPTION INHIBITORS

(57) Abstract

This invention relates to a compound of formula (I) wherein: R^1 is lower alkyl, aryl, a heterocyclic group, etc., R^2 is hydrogen, lower alkyl, etc., R^3 is hydrogen or lower alkyl, R^4 is hydrogen, halogen, lower alkyl, etc., R^5 and R^6 are each hydrogen, etc., R^7 is a heterocyclic group or aryl, each of which may be substituted with substituent(s), X is O or S, and Y is –NHCO–, etc., and pharmaceutically acceptable salt thereof, to processes for preparation thereof, to a pharmaceutical composition comprising the same, and to a method for the prevention and/or the treatment of bone diseases caused by abnormal bone metabolism in human being or animals.



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DESCRIPTION

QUINOLINE DERIVATIVES AS H^+-ATPase INHIBITORS AND AS BONE RESORPTION INHIBITORS

Technical Field

This invention relates to new heterocyclic compounds and pharmaceutically acceptable salts thereof.

More particularly, it relates to new heterocyclic compounds and pharmaceutically acceptable salts thereof which have inhibitory activities of vacuolar type H^+-adenosine triphosphatases (H^+-ATPases), especially osteoclast H^+-ATPase, and inhibitory activities of bone resorption, and therefore are useful for the prevention and/or the treatment of bone diseases caused by abnormal bone metabolism in human being or animals as the inhibitors of bone resorption or the inhibitors of bone metastasis.

And further, the present invention relates to processes for the preparation of said compounds, to a pharmaceutical composition comprising the same and to a method for the prevention and/or the treatment of above-mentioned diseases in human being or animals, and to a use of said compounds and pharmaceutically acceptable salts thereof for the prevention and/or the treatment of above-mentioned diseases in human being or animals.

Background Art

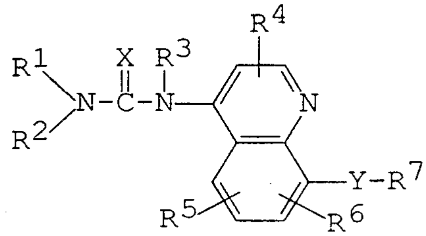
Some heterocyclic compounds have been known as described in, for example, J. Chem. Soc. Pak. (1995), 17(4), 232-6; J. Am. Chem. Soc. (1994), 116(24), 11014-19; or Chem. Pharm. Bull. (1990), 38(10), 2841-6. However, it is not known that said compounds have inhibitory activities of vacuolar type H^+-ATPases or inhibitory activities of bone resorption.

Heterocyclic compounds having inhibitory activities of vacuolar type H^+-ATPases or inhibitory activities of bone

resorption have been known as described in WO 97/14681.

Disclosure of the Invention

The object heterocyclic compounds of this invention are new and can be represented by the following general formula [I] :



[I]

wherein

R^1 is hydrogen; lower alkyl which may be substituted with substituent(s) selected from the group consisting of hydroxy, lower alkoxy, acyl, cyclo(lower)alkyl, halogen, aryl and a heterocyclic group;
lower alkenyl; cyclo(lower)alkyl;
amino; lower alkylamino;
substituted or unsubstituted aryl; or
substituted or unsubstituted heterocyclic group;
and

R^2 is hydrogen; or lower alkyl which may be substituted with a substituent selected from the group consisting of hydroxy and lower alkoxy;
or

R^1 and R^2 are taken together with the attached nitrogen atom to form substituted or unsubstituted N-containing heterocyclic-N-yl group,

R^3 is hydrogen or lower alkyl,

R^4 is hydrogen, halogen, cyano or
lower alkyl which may be substituted with a substituent selected from the group consisting of hydroxy and lower

alkoxy,

R^5 and R^6 are each hydrogen, halogen, lower alkyl, lower alkoxy or halo(lower)alkyl,

R^7 is a heterocyclic group or aryl, each of which may be substituted with substituent(s) selected from the group consisting of halogen, nitro, lower alkyl, lower alkoxy, hydroxy, ar(lower)alkoxy and halo(lower)alkyl,

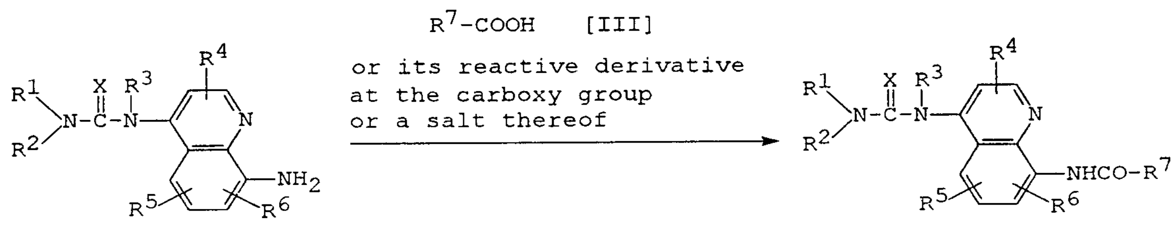
X is O or S,

and

Y is -NHCO-, -CONH- or $-NH\overset{\overset{X^1}{\|}}{C}NH-$, in which X^1 is O or S.

The object compound [I] or its salt can be prepared by processes as illustrated in the following reaction schemes.

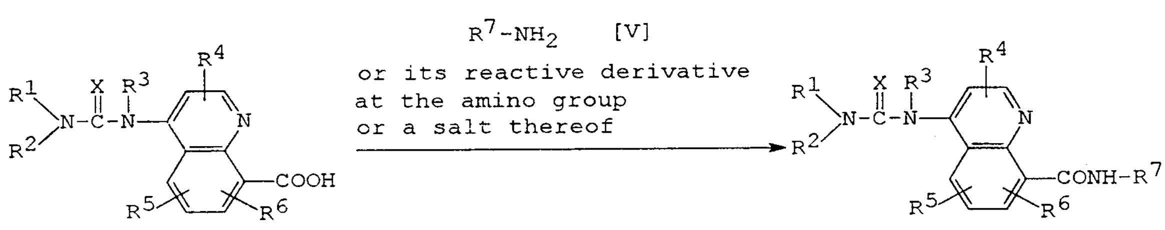
Process 1



[II]
or its reactive derivative at the amino group or a salt thereof

[Ia]
or its salt

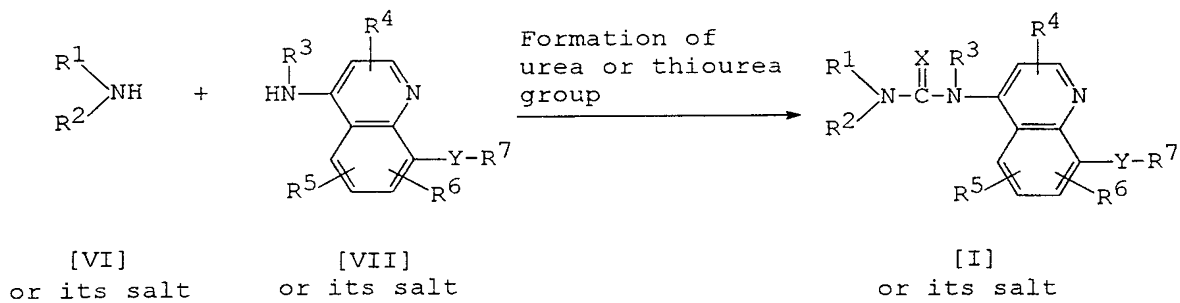
Process 2



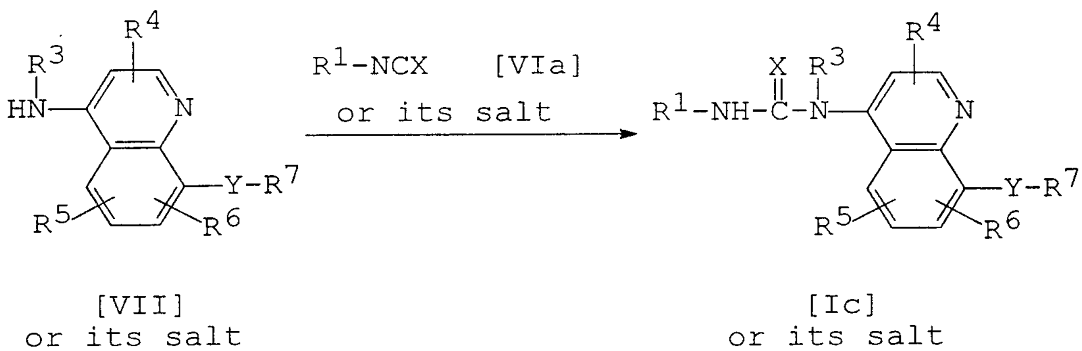
[IV]
or its reactive derivative at the carboxy group or a salt thereof

[Ib]
or its salt

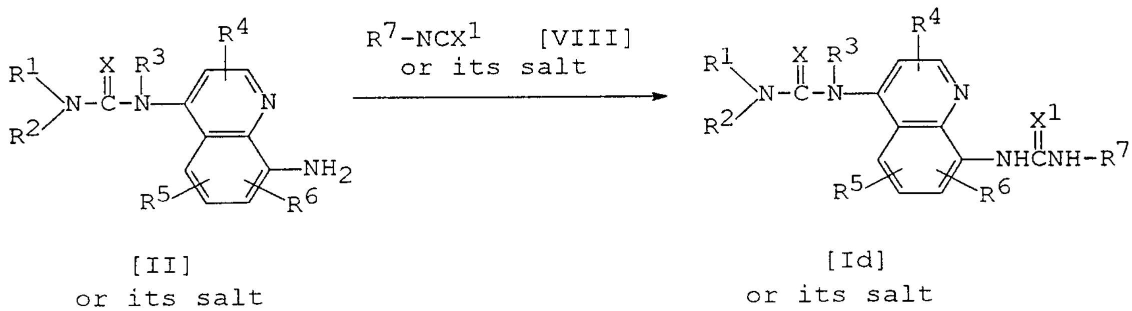
Process 3



Process 4



Process 5



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, X, X^1 and Y are each as defined above.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

In this respect, the term "lower" in lower alkenyl moiety in the various definitions is intended to mean a group having 2 to 6 carbon atoms.

The term "lower" in cyclo(lower)alkyl moiety in the various definitions is intended to mean a group having 3 to 6 carbon atoms.

Suitable "lower alkyl" and all lower alkyl moieties in the various definitions mentioned in this specification and claims such as in the terms "heterocyclic(lower)alkyl", "hydroxy(lower)alkyl", "lower alkoxy(lower)alkyl", etc., may be straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, 1-ethylpropyl, sec-butyl, hexyl or the like, in which preferable one is C_1-C_4 alkyl such as methyl, ethyl, propyl, isobutyl or tert-butyl.

Suitable "lower alkoxy" and lower alkoxy moiety in the term "lower alkoxy(lower)alkyl" may be straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy or the like, in which preferable one is C_1-C_4 alkoxy such as methoxy, ethoxy or isopropoxy.

Suitable "acyl" and acyl moiety in the term "acyl(lower)alkyl", may be lower alkanoyl [e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, 3,3-dimethylbutyryl, etc.], heterocyclic(lower)alkanoyl [e.g. thienylacetyl, imidazolylacetyl, pyridylacetyl, pyridylpropionyl, etc.], carboxy, esterified carboxy such as lower alkoxycarbonyl

[e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.], etc., heterocycliccarbonyl which may be substituted with substituent [e.g. furoyl, thenoyl, pyridylcarbonyl, imidazolylcarbonyl, morpholinocarbonyl, piperidinocarbonyl, 1-methylimidazolylcarbonyl, 4-methyl-1-piperazinylcarbonyl, 4-ethyl-1-piperazinylcarbonyl, dimethylaminopiperidino-carbonyl, 4-methylcarbamoyl-1-piperazinylcarbonyl, 4-acetyl-1-piperazinylcarbonyl, 4-phenyl-1-piperazinylcarbonyl, chlorothenoyl, 1,2,3,6-tetrahydropyridylcarbonyl, pyrrolidinylcarbonyl, indolylcarbonyl, etc.], aroyl which may be substituted with substituent(s) [e.g. benzoyl, naphthoyl, methoxybenzoyl, dichlorobenzoyl, trifluoromethylbenzoyl, etc.], substituted or unsubstituted carbamoyl such as carbamoyl, lower alkylcarbamoyl [e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, isobutylcarbamoyl, tert-butylcarbamoyl, pentylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, N-ethyl-N-methylcarbamoyl, etc.], substituted or unsubstituted arylcarbamoyl, for example, arylcarbamoyl [e.g. phenylcarbamoyl, tolylcarbamoyl, xylylcarbamoyl, naphthylcarbamoyl, ethylphenylcarbamoyl, etc.], halo(lower)alkyl-arylcarbamoyl [e.g. trifluoromethylphenylcarbamoyl, etc.], etc., heterocycliccarbamoyl [e.g. pyridylcarbamoyl, imidazolylcarbamoyl, pyrazolylcarbamoyl, etc.], N-heterocyclic-N-(lower alkyl)carbamoyl [e.g. N-pyridyl-N-methylcarbamoyl, etc.], substituted or unsubstituted heterocyclic(lower)alkylcarbamoyl, for example, heterocyclic(lower)alkylcarbamoyl [e.g. pyridylmethylcarbamoyl, pyridylethylcarbamoyl, oxadiazolylmethylcarbamoyl, furylmethylcarbamoyl, thienylmethylcarbamoyl, tetrahydrofurylmethylcarbamoyl, piperonylmethylcarbamoyl, indolylethylcarbamoyl,

imidazolylethylcarbamoyl, etc.], lower alkyl-heterocyclic(lower)alkylcarbamoyl [e.g. methylpyridylmethyl-carbamoyl, methyloxadiazolylmethylcarbamoyl, etc.], etc., etc., lower alkylsulfonyl [e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, etc.], arylsulfonyl [e.g. phenylsulfonyl, tolylsulfonyl, etc.], or the like.

Suitable "cyclo(lower)alkyl" and cyclo(lower)alkyl moiety in the term "cyclo(lower)alkyl(lower)alkyl" may be cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Suitable "aryl" may be phenyl, naphthyl, fluorenyl, phenyl substituted with lower alkyl [e.g. tolyl, xylyl, mesityl, cumenyl, di(tert-butyl)phenyl, etc.] and the like, in which preferable one is phenyl, naphthyl and tolyl.

Suitable "heterocyclic group" and heterocyclic moieties in the term "heterocyclic(lower)alkyl" may include saturated or unsaturated, monocyclic or polycyclic one containing at least one hetero atom such as nitrogen atom, oxygen atom or sulfur atom, preferably N,O and/or S containing heterocyclic group, in which preferable ones may be morpholinyl, thiomorpholinyl, piperazinyl, pyridyl, dihydropyridyl, tetrahydropyridyl, pyrimidinyl, hexahydropyrimidinyl, pyrazinyl, pyridazinyl, piperidyl, thienyl, furyl, tetrahydrofuryl, oxazolyl, oxazolidinyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, pyrrolyl, oxiranyl, tetrahydrofuryl, piperonyl, indolyl, quinolyl, isoquinolyl, benzimidazolyl, benzimidazolidinyl, benzoxazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolidinyl, imidazo[4,5-b]-pyridyl, or the like.

Suitable "lower alkenyl" may be vinyl, allyl, 1-propenyl, methylpropenyl, butenyl, pentenyl or the like.

Suitable "lower alkylamino" is mono- or di- lower alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, pentylamino, hexylamino,

dimethylamino, diethylamino, ethylmethylamino, or the like.

Suitable substituents of aryl in the term "substituted or unsubstituted aryl" may be halogen, nitro, amino, hydroxy(lower)alkyl [e.g. hydroxymethyl, hydroxyethyl, 1-hydroxy-methylethyl, etc.], lower alkyl, halo(lower)alkyl, acyl [e.g. lower alkanoyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, etc.], lower alkoxy, lower alkylthio, or the like.

Suitable substituents of a heterocyclic group in the terms "substituted or unsubstituted heterocyclic group" or "substituted or unsubstituted N-containing heterocyclic-N-yl group" may be halogen, lower alkyl, hydroxy(lower)alkyl [e.g. hydroxymethyl, hydroxyethyl, etc.], lower alkoxy(lower)alkyl [e.g. methoxymethyl, methoxyethyl, ethoxyethyl, etc.], oxo, thioxo, hydroxy, acyl [e.g. lower alkanoyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, etc.], or the like.

Suitable "N-containing heterocyclic-N-yl group" may be morpholino, thiomorpholino, pyrrolidin-1-yl, piperidino, 1,2,3,6-tetrahydropyridin-1-yl, piperazin-1-yl, imidazol-1-yl, imidazolin-1-yl, imidazolidin-1-yl, benzimidazol-1-yl, benzimidazolidin-1-yl, pyrazol-1-yl, pyrazolidin-1-yl, hexahydropyrimidin-1-yl, oxazolidin-1-yl, or the like.

Suitable "halogen" may be fluorine, chlorine, bromine and iodine.

Suitable "halo(lower)alkyl" may be chloromethyl, bromoethyl, dichloromethyl, difluoromethyl, trifluoromethyl, trifluoroethyl, pentafluoropropyl, or the like, in which preferable compounds are trifluoromethyl, trifluoroethyl and pentafluoropropyl.

Suitable "ar(lower)alkoxy" may be benzyloxy, phenethyloxy, benzhydryloxy, trityloxy or the like, in which the most preferable one is benzyloxy.

Suitable "ar(lower)alkyl" may be benzyl, phenethyl, benzhydryl, trityl, naphthylmethyl or the like.

Suitable pharmaceutically acceptable salts of the object compound [I] are conventional non-toxic salts and include a metal salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc.] and an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.], an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, oxalate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], a salt with an amino acid [e.g. arginine salt, aspartic acid salt, glutamic acid salt, etc.], an intramolecular salt and the like.

With respect to the salts of the compounds [Ia] to [Id] in the Processes 1, 2, 4 or 5, it is to be noted that those compounds are included within the scope of the compound [I], and accordingly the suitable examples of the salts of these compounds are to be referred to those as exemplified for the object compound [I].

Preferred embodiments of the object compound [I] are as follows :

R^1 is - hydrogen,

- lower alkyl which may be substituted with one or more substituents selected from the group consisting of hydroxy, lower alkoxy, acyl, cyclo(lower)alkyl, halogen, aryl and a heterocyclic group [more preferably, lower alkyl, hydroxy(lower)alkyl, lower alkoxy(lower)alkyl, carboxy(lower)alkyl, esterified carboxy(lower)alkyl (e.g. lower alkoxycarbonyl(lower)alkyl, etc.), cyclo(lower)alkyl-(lower)alkyl, halo(lower)alkyl, ar(lower)alkyl (e.g.

benzyl, phenethyl, etc.) or heterocyclic(lower)alkyl (e.g. pyridyl(lower)alkyl, piperidyl(lower)alkyl, etc.)],

- lower alkenyl,
- cyclo(lower)alkyl,
- amino,
- lower alkylamino,
- substituted or unsubstituted aryl [more preferably, phenyl or naphthyl, each of which may be substituted with substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halo(lower)alkyl, acyl (e.g. lower alkoxycarbonyl, etc.), nitro, amino and halogen],

  or
- substituted or unsubstituted heterocyclic group [more preferably, pyridyl, pyrimidinyl, quinolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, morpholinyl, thienyl, tetrahydrofuryl or pyrrolidinyl, each of which may be substituted with substituent(s) selected from the group consisting of lower alkyl, halogen, oxo and acyl (e.g. lower alkoxycarbonyl, etc.)],

  and

R^2 is hydrogen or lower alkyl which may be substituted with a substituent selected from the group consisting of hydroxy and lower alkoxy, or

R^1 and R^2 are taken together with the attached nitrogen atom to form substituted or unsubstituted N-containing heterocyclic-N-yl group [more preferably, morpholino, thiomorpholino, piperidino, 1-piperazinyl or 1-pyrrolidinyl, each of which may be substituted with a substituent selected from the group consisting of lower alkyl and acyl (e.g. lower alkanoyl, etc.)],

R^3 is hydrogen or lower alkyl,

R^4 is hydrogen, halogen, cyano or lower alkyl which may be substituted with a substituent selected from the group consisting of hydroxy and lower alkoxy [more preferably, hydrogen, halogen, cyano, lower alkyl or lower alkoxy(lower)alkyl],

R^5 is hydrogen, halogen, lower alkyl, lower alkoxy or halo(lower)alkyl [more preferably, hydrogen],

R^6 is hydrogen, halogen, lower alkyl, lower alkoxy or halo(lower)alkyl [more preferably, hydrogen],

R^7 is a heterocyclic group or aryl, each of which may be substituted with substituent(s) selected from the group consisting of halogen, nitro, lower alkyl, lower alkoxy, hydroxy, ar(lower)alkoxy and halo(lower)alkyl [more preferably, phenyl substituted with one or two halogen(s); phenyl substituted with nitro; phenyl substituted with halo(lower)alkyl; phenyl substituted with halo(lower)alkyl and hydroxy; phenyl substituted with one or two halogen(s) and hydroxy; phenyl substituted with one or two or three hydroxy; phenyl substituted with one or two or three benzyloxy; naphthyl; quinolyl; pyridyl; pyrazinyl; pyridyl substituted with hydroxy; pyridyl substituted with one or two lower alkyl; pyridyl substituted with lower alkoxy; pyridyl substituted with halo(lower)alkyl; pyridyl substituted with one or two halogen(s) and lower alkyl; or
pyridyl substituted with one or two halogen(s)],

X is O or S,

and

Y is -NHCO-, -CONH- or $-NH\overset{\overset{\large X^1}{\|}}{C}NH-$,
in which X^1 is O or S
[more preferably, -NHCO-].

The processes for preparing the object compound [I] are explained in detail in the following.

Process 1

The object compound [Ia] or its salt can be prepared by reacting a compound [II] or its reactive derivative at the amino group or a salt thereof with a compound [III] or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the amino group of the compound [II] may be a silyl derivative formed by the reaction of the compound [II] with a silyl compound such as bis(trimethylsilyl)acetamide or mono(trimethylsilyl)-acetamide, or the like.

Suitable salts of the compound [II] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

Suitable reactive derivative at the carboxy group of the compound [III] may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like.

Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as dialkylphosphoric acid, sulfuric acid, aliphatic carboxylic acid or aromatic carboxylic acid; a symmetrical acid anhydride; an activated amide with imidazole; or an activated ester [e.g. p-nitrophenyl ester, etc.]. These reactive derivatives can optionally be selected from them according to the kind of the compound [III] to be used.

Suitable salts of the compound [III] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

The reaction is usually carried out in a conventional solvent, such as methylene chloride, chloroform, ethylene chloride, pyridine, dioxane, tetrahydrofuran, N,N-dimethylformamide, or the like.

In case that the compound [III] is used in the free acid form or salt form, it is preferable to carry out the reaction in the presence of a conventional condensing agent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, N,N'-dicyclohexylcarbodiimide, diphenyl chlorophospate or the like.

The reaction temperature is not critical and the reaction can be carried out under cooling, at ambient temperature, or under heating.

This reaction is preferably carried out in the presence of a conventional inorganic base or in the presence of a conventional organic base.

Process 2

The object compound [Ib] or its salt can be prepared by reacting a compound [IV] or its reactive derivative at the carboxy group or a salt thereof with a compound [V] or its reactive derivative at the amino group or a salt thereof.

Suitable salts of the compounds [IV] and [V] and their reactive derivatives can be referred to the ones as exemplified for the compound [I].

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction condition of this reaction are to be referred to those explained in Process 1.

Process 3

The object compound [I] or its salt can be prepared by subjecting a compound [VI] or its salt and a compound [VII] or its salt to a formation reaction of urea or thiourea group.

Suitable salts of the compounds [VI] and [VII] may be the same as those exemplified for the compound [I].

This reaction is usually carried out in the presence of a reagent which introduces a carbonyl or thiocarbonyl group

such as phosgene, triphosgen, haloformate compound [e.g. ethyl chloroformate, trichloromethyl chloroformate, phenyl chloroformate etc.], 1,1'-carbonyldiimidazole, 1,1'-thiocarbonyldiimidazole, or the like.

This reaction is usually carried out in a solvent such as dioxane, tetrahydrofuran, benzene, toluene, chloroform, methylene chloride, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The compound [I] or its salt can be also prepared by reacting a compound [VI] or its salt with the reagent which introduces a carbonyl or thiocarbonyl group as mentioned above and then by reacting the obtained compound with a compound [VII] or its salt, or by reacting a compound [VII] or its salt with said reagent and then by reacting the obtained compound with a compound [VI] or its salt. These processes are also included within the scope of this process.

Process 4

The object compound [Ic] or its salt can be prepared by reacting a compound [VII] or its salt with a compound [VIa] or its salt.

Suitable salts of the compound [VIa] may be the same as those exemplified for the compound [VI].

This reaction is usually carried out in a conventional solvent such as dichloroethane, tetrahydrofuran, dioxane, N,N-dimethylformamide, N-methylpyrrolidone, toluene or the like.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under warming or heating.

Process 5

The object compound [Id] or its salt can be prepared by reacting a compound [II] or its salt with a compound [VIII] or its salt.

Suitable salts of the compounds [II] and [VIII] can be referred to the ones as exemplified for the compound [I].

This reaction is usually carried out in a conventional solvent such as dichloroethane, tetrahydrofuran, dioxane, N,N-dimethylformamide, N-methylpyrrolidone, toluene or the like.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under warming or heating.

The object compound [I] and the starting compounds can also be prepared by the methods of Examples mentioned below or similar manners thereto or conventional manners.

The compound obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, chromatography, reprecipitation or the like.

It is to be noted that the compound [I] and the other compounds may include one or more stereoisomers and geometrical isomers due to asymmetric carbon atoms and double bonds, and all of such isomers and mixture thereof are included within the scope of this invention.

The compound of the formula [I] and its salt can be in the form of a solvate, which is included within the scope of the present invention. The solvate preferably includes a hydrate and an ethanolate.

The object compound [I] and pharmaceutically acceptable salts thereof have inhibitory activities of vacuolar type H^+-ATPases, especially osteoclast H^+-ATPase, and inhibitory activities of bone resorption, and therefore are useful for the prevention and/or the treatment of bone diseases caused by abnormal bone metabolism such as osteoporosis (especially,

postmenopausal osteoporosis); hypercalcemia; hyperparathyroidism; Paget's bone diseases; osteolysis; hypercalcemia of malignancy with or without bone metastasis; rheumatoid arthritis; periodontitis; osteoarthritis; ostealgia; osteopenia; cancer cachexia; malignant tumor; or the like in human being or animals as the inhibitors of bone resorption or the inhibitors of bone metastasis.

Further, it is expected that the object compound [I] and pharmaceutically acceptable salts thereof of the present invention are useful for the prevention and/or the treatment of tumors, especially those related to renal cancer, melanoma, colon cancer, lung cancer and leukemia; viral conditions (e.g. those involving *Semliki Forest, Vesicular Stomatitis, Newcastle Disease, Influenza A* and *B, HIV* viruses); ulcers (e.g. chronic gastritis and peptic ulcer induced by *Helicobacter pylori*); autoimmune diseases; transplantation; hypercholesterolemic and atherosclerotic diseases; AIDS; Alzheimer's disease; angiogenic diseases such as diabetic retinopathy, psoriasis and solid tumors; or the like in human being or animals, and useful for regulating male fertility in human being or animals.

In order to illustrate the usefulness of the object compound [I], the pharmacological test data of some representative compounds of the compound [I] are shown in the following.

<u>Test 1</u> (Inhibition of vacuolar type H^+-ATPase proton transport) :

<u>Test Method</u>

(a) Preparation of microsomes from mouse peritoneal macrophages

Seven-week-old male ddY mice were injected

intraperitoneally with 2 ml of 3% thioglycolate medium. After 3-5 days, the mice were decapitated, and the peritoneal macrophages were obtained by peritoneal lavage with 5-6 ml of Hanks' balanced salt solution (HBSS). The cells were washed twice with cold HBSS. Vesicles were prepared from the cells, homogenized in a Douncee homogenizer (20 strokes) in 10 ml of 250 mM sucrose, 5 mM Tris, 1 mM EGTA, 1 mM $KHCO_3$ and 1 mM dithiothreitol, pH 7.0, at 4°C. After an initial centrifugation (1000 x g for 5 minutes), the supernatant was centrifuged 6000 x g for 15 minutes) to remove mitochondria and lysosomes. The supernatant was centrifuged at 42000 x g for 30 minutes, and microsomal pellet was collected and stored at -80°C.

(b) Measurement of proton transport

Proton transport was assayed with a dual-wavelength spectrophotometer by monitering uptake of acridine orange (Reference 540 nm, Measurement 492 nm) [H.C. Blair, J. Cell. Biol., 102, 1164 (1986)] with aliquot of membrane vesicles suspended in 300 ml of assay buffer containing 150 mM KCl, 10 mM bis-tris-propane, 2 mM $MgCl_2$, 10 mM acridine orange, 1 mM valinomycin, 10 mg/ml oligomycin and test compounds (concentration : 1×10^{-6}M), pH 7.0. The reaction was initiated by addition of 1 mM ATP. Results were expressed as the percent of control.

Test Results

Test Compound (Example No.)	Inhibition (%) of vacuolar type H^+-ATPase proton transport
4-(1)	96
4-(15)	93
4-(20)	92
4-(23)	92
4-(45)	91

Test 2 (Bone organ culture) :

Test Method

Calvariae from Wistar rats were excised and cultured in wells of 12-well culture plates containing 2 ml of Dulbecco's modified minimum essential medium supplemented with 10% fetal bovine serum and 10^{-8}M human parathyroid hormone fragment (1-34) [PTH] in the presence of the test compound (concentration : 1×10^{-6}M). In control dishes, PTH was not added. Control and PTH control were exposed to an equivalent concentration of the vehicle. Six days later, the concentration of calcium ([Ca]) in the medium was measured by methylxylenol blue method and the percentage of inhibition of PTH-induced bone resorption was calculated according to following formula :

$$\text{Inhibition (\%)} = \frac{C_P - C_D}{C_P - C_0} \times 100$$

C_P : [Ca] in PTH control dishes
C_D : [Ca] in the test compound dishes
C_0 : [Ca] in control dishes

Test Results

Test Compound (Example No.)	Inhibition (%) of PTH-induced bone resorption
4-(1)	100
4-(15)	91
4-(20)	96
4-(23)	92
4-(45)	100

For therapeutic purpose, the compound [I] and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid, semi-solid or liquid excipient suitable for oral, parenteral such as intravenous, intramuscular, subcutaneous or intraarticular, external such as topical, enteral, intrarectal, transvaginal, inhalant, ophthalmic, nasal or hypoglossal administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, suppositories, solution, lotion, suspension, emulsion, ointment, gel, cream, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound [I] will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound [I] may be effective for preventing and/or treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

Examples

The following Examples are given for the purpose of illustrating this invention.

Example 1

(1) To a suspension of 4-chloro-8-(2,6-dichlorobenzoyl-amino)quinoline (7.0 g) in dimethyl sulfoxide (100 ml) was added sodium azide (5.18 g), and the mixture was stirred at 90°C for 4 hours. The resulting solution was diluted with water (200 ml), and the solid was collected by filtration under reduced pressure and washed with water (100 ml) to give 4-azido-8-(2,6-dichlorobenzoylamino)quinoline (6.75 g) as a brown solid.

NMR (DMSO-d_6, δ) : 7.48-7.62 (4H, m), 7.67 (1H, t, J=8Hz), 7.82 (1H, d, J=8Hz), 8.77 (1H, d, J=8Hz), 8.83 (1H, d, J=5Hz)

(2) A suspension of 4-azido-8-(2,6-dichlorobenzoylamino)-quinoline (6.75 g) and triphenylphosphine (4.99 g) in ethyl acetate (80 ml) was stirred at 45°C for 3.5 hours. The solvent was removed in vacuo, and the residue was treated with hot ethanol (50 ml). The mixture was cooled to ambient temperature, and the solid was collected by filtration under reduced pressure and washed with ethanol (25 ml) to give 8-(2,6-dichlorobenzoylamino)-4-[N-(triphenylphosphoranylidene)-amino]quinoline (10.4 g) as a colorless crystal.

NMR (DMSO-d_6, δ) : 6.17 (1H, d, J=6Hz), 7.47-7.74 (13H, m), 7.81-7.91 (6H, m), 8.08 (1H, d, J=6Hz), 8.53 (1H, d, J=9Hz), 8.62 (1H, d, J=9Hz)

(3) A suspension of 8-(2,6-dichlorobenzoylamino)-4-[N-(triphenylphosphoranylidene)amino]quinoline (10.4 g) in 6N hydrochloric acid (100 ml) and acetic acid (80 ml) was refluxed for 30 minutes. The resulting mixture was cooled to ambient temperature and neutralized with 6N sodium hydroxide aqueous solution. The solid was collected by filtration under reduced pressure and washed with water (50 ml). The resulting solid was treated with hot ethyl acetate (30 ml) and the mixture was cooled to ambient temperature. The solid

was collected by filtration in vacuo and washed with water to afford 4-amino-8-(2,6-dichlorobenzoylamino)quinoline (5.85 g) as a white powder.

NMR (DMSO-d_6, δ) : 6.88 (1H, d, J=8Hz), 7.51-7.63 (3H, m), 7.75 (1H, t, J=8Hz), 8.34 (1H, d, J=8Hz), 8.40 (1H, d, J=8Hz), 8.52 (1H, d, J=8Hz), 9.13-9.33 (2H, m)

(4) A mixture of 4-amino-8-(2,6-dichlorobenzoylamino)-quinoline (3.0 g) and phenyl chloroformate (2.12 g) in pyridine (80 ml) was stirred for 30 minutes at ambient temperature. The mixture was concentrated in vacuo, water was added to the residue. The mixture was extracted with ethyl acetate, and the extract was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (n-hexane-ethyl acetate). The residue was treated with hot ethanol, and the mixture was cooled to ambient temperature. The precipitate was collected by filtration and washed with ethanol to give 8-(2,6-dichlorobenzoylamino)-4-(phenoxycarbonylamino)quinoline (2.0 g) as slight yellow powder.

NMR ($CDCl_3$, δ) : 7.20-7.50 (8H, m), 7.60-7.71 (2H, m), 7.88-7.98 (1H, br s), 8.23 (1H, d, J=7Hz), 8.70 (1H, d, J=7Hz), 8.98-9.07 (1H, m)

(5) To a solution of 8-(2,6-dichlorobenzoylamino)-4-(phenoxycarbonylamino)quinoline (60 mg) in N,N-dimethylformamide (2.0 ml) was added 2.0M solution of dimethylamine in tetrahydrofuran (0.14 ml) at ambient temperature, and the solution was stirred for 5 minutes. The mixture was diluted with ethyl acetate (10 ml) and washed with water and brine successively. The organic layer was dried over magnesium sulfate, and the solvent was removed in vacuo. The residue was treated with hot ethanol (1.0 ml),

and the mixture was cooled to ambient temperature. The solid was collected by filtration under reduced pressure and washed with ethanol (1.5 ml) to give 8-(2,6-dichlorobenzoylamino)-4-(3,3-dimethylureido)quinoline (31 mg) as a yellow crystal.

mp : 242-244°C

NMR (DMSO-d_6, δ) : 3.07 (6H, s), 7.48-7.65 (4H, m), 7.87 (1H, d, J=4Hz), 7.97 (1H, d, J=8Hz), 8.67-8.76 (3H, m), 10.68 (1H, s)

Example 2

The following compounds were obtained according to a similar manner to that of Example 1-(5).

(1) 8-(2,6-Dichlorobenzoylamino)-4-(3-ethyl-3-methylureido)-quinoline

(from 8-(2,6-dichlorobenzoylamino)-4-(phenoxycarbonylamino)quinoline and N-ethylmethylamine)

mp : 229-231°C

NMR (DMSO-d_6, δ) : 1.15 (3H, t, J=9Hz), 3.08 (3H, s), 3.46 (2H, q, J=9Hz), 7.48-7.64 (4H, m), 7.84 (1H, d, J=4Hz), 7.93 (1H, d, J=9Hz), 8.67-8.74 (3H, m)

(2) 8-(2,6-Dichlorobenzoylamino)-4-(3,3-diethylureido)-quinoline

(from 8-(2,6-dichlorobenzoylamino)-4-(phenoxycarbonylamino)quinoline and diethylamine)

mp : 225-229°C

NMR ($CDCl_3$, δ) : 1.34 (6H, t, J=8Hz), 3.50 (4H, q, J=8Hz), 7.25-7.36 (2H, m), 7.38-7.44 (3H, m), 7.60 (1H, t, J=8Hz), 8.30 (1H, d, J=4Hz), 8.63 (1H, d, J=4Hz), 8.97 (1H, d, J=8Hz)

Example 3

(1) 4-Azido-8-(2,6-dichlorobenzoylamino)-3-methylquinoline was obtained from 4-chloro-8-(2,6-dichlorobenzoylamino)-

3-methylquinoline and sodium azide according to a similar manner to that of Example 1-(1).

NMR (DMSO-d_6, δ) : 2.60 (3H, s), 7.48-7.59 (3H, m), 7.67 (1H, t, J=8Hz), 7.90 (1H, d, J=8Hz), 8.68 (1H, s), 8.69 (1H, d, J=8Hz)

(2) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[N-(triphenylphosphoranylidene)amino]quinoline was obtained according to a similar manner to that of Example 1-(2).

NMR (DMSO-d_6, δ) : 1.98 (3H, s), 7.15 (1H, t, J=8Hz), 7.48-7.73 (18H, m), 7.78 (1H, dd, J=2, 8Hz), 8.34 (1H, s), 8.47 (1H, dd, J=8Hz)

(3) 4-Amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline was obtained according to a similar manner to that of Example 1-(3).

NMR (DMSO-d_6, δ) : 2.28 (3H, s), 7.53 (1H, dd, J=6, 9Hz), 7.57-7.62 (2H, m), 7.72 (1H, t, J=9Hz), 8.38-8.46 (2H, m), 8.52 (1H, d, J=9Hz)

(4) To a solution of 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline (100 mg) and triethylamine (175 mg) in dichloroethane (3.0 ml) was added triphosgene (85.7 mg), and the mixture was stirred at ambient temperature for 20 minutes. To the mixture was added 2.0M solution of methylamine in tetrahydrofuran (0.3 ml), and the resulting mixture was stirred at ambient temperature for 20 minutes. The resulting mixture was diluted with chloroform (10 ml) and washed with water and saturated sodium bicarbonate aqueous solution successively. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was treated with ethanol, and then the solid was collected by filtration under reduced pressure and washed with ethanol to give 8-(2,6-dichlorobenzoylamino)-3-methyl-4-(3-methylureido)quinoline (37 mg) as a yellow crystal.

mp : 265-266°C

NMR ($CDCl_3$, δ) : 1.82-1.90 (2H, m), 2.46 (3H, s), 2.80 (3H, s), 7.35 (1H, dd, J=7, 9Hz), 7.38-7.44 (2H, m), 7.60 (1H, t, J=9Hz), 7.72 (1H, d, J=9Hz), 8.66 (1H, s), 8.89 (1H, d, J=9Hz)

Example 4

The following compounds were obtained according to a similar manner to that of Example 3-(4).

(1) 8-(2,6-Dichlorobenzoylamino)-4-(3,3-dimethylureido)-3-methylquinoline

(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 2M solution of dimethylamine in tetrahydrofuran)

mp : 236-239°C

NMR ($CDCl_3$, δ) : 2.38 (3H, s), 3.13 (6H, s), 6.47 (1H, s), 7.28-7.34 (1H, m), 7.38 (2H, d, J=8Hz), 7.55 (1H, t, J=8Hz), 7.59 (1H, d, J=8Hz), 8.59 (1H, s), 8.84 (1H, d, J=8Hz), 10.07 (1H, s)

(2) 8-(2,6-Dichlorobenzoylamino)-4-(3-ethylureido)-3-methylquinoline

(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and ethylamine hydrochloride)

mp : 247.5-248°C

NMR (DMSO-d_6, δ) : 1.09 (3H, t, J=7.5Hz), 2.33 (3H, s), 3.13 (2H, m), 6.41 (1H, t, J=5.0Hz), 7.48-7.65 (4H, m), 7.75 (1H, d, J=7.5Hz), 8.59 (1H, s), 8.62 (1H, d, J=7.5Hz), 8.71 (1H, s)

(3) 8-(2,6-Dichlorobenzoylamino)-4-(3-ethyl-3-methylureido)-3-methylquinoline

(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and N-ethylmethylamine)

mp : 220-223°C

NMR ($CDCl_3$, δ) : 1.29 (3H, t, J=8Hz), 2.38 (3H, s), 3.12 (3H, s), 3.50 (2H, q, J=8Hz), 6.46 (1H, s), 7.28-7.41 (3H, m), 7.52-7.60 (2H, m), 8.59 (1H, s), 8.82-8.87 (1H, m), 10.07 (1H, s)

(4) 8-(2,6-Dichlorobenzoylamino)-4-(3,3-diethylureido)-3-methylquinoline

(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and diethylamine)

mp : 241-244°C

NMR ($CDCl_3$, δ) : 1.31 (6H, t, J=7Hz), 2.38 (3H, s), 3.48 (4H, q, J=7Hz), 6.46 (1H, s), 7.30 (1H, dd, J=7, 9Hz), 7.37-7.41 (2H, m), 7.54-7.59 (2H, m), 8.59 (1H, s), 8.82-8.88 (1H, m)

(5) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-(3-n-propylureido)quinoline

(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and n-propylamine)

mp : 242-244°C

NMR (DMSO-d_6, δ) : 0.90 (3H, t, J=8Hz), 1.49 (2H, q, J=8Hz), 2.33 (3H, s), 3.09 (2H, q, J=8Hz), 6.44 (1H, t, J=7Hz), 7.48-7.64 (4H, m), 7.74 (1H, d, J=9Hz), 8.58 (1H, s), 8.62 (1H, d, J=8Hz), 8.71 (1H, s)

(6) 8-(2,6-Dichlorobenzoylamino)-4-(3-isopropylureido)-3-methylquinoline

(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and isopropylamine)

mp : 234-235°C

NMR (DMSO-d_6, δ) : 1.14 (6H, d, J=7.5Hz), 2.32 (3H, s), 3.78 (1H, m), 6.31 (1H, d, J=7.5Hz), 7.51 (1H, dd, J=8.5, 7.0Hz), 7.56-7.65 (3H, m), 7.74 (1H, d,

J=7.5Hz), 8.48 (1H, s), 8.63 (1H, d, J=7.5Hz), 8.71 (1H, s)

(7) 4-(3-Allylureido)-8-(2,6-dichlorobenzoylamino)-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and allylamine)
mp : 242-243°C
NMR (DMSO-d_6, δ) : 2.35 (3H, s), 3.76 (2H, dd, J=5.0, 5.0Hz), 5.10 (1H, d, J=9.0Hz), 5.22 (1H, d, J=16.0Hz), 5.83-5.96 (1H, m), 6.58 (1H, t, J=5.0Hz), 7.48-7.64 (4H, m), 7.76 (1H, d, J=8.0Hz), 8.63 (1H, d, J=8.0Hz), 8.67 (1H, s), 8.73 (1H, s), 10.70 (1H, s)

(8) 4-(3-n-Butylureido)-8-(2,6-dichlorobenzoylamino)-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and n-butylamine)
mp : 235-239°C
NMR (DMSO-d_6, δ) : 0.92 (3H, t, J=7Hz), 1.29-1.50 (4H, m), 2.33 (3H, s), 3.12 (2H, q, J=7Hz), 6.42 (1H, t, J=7Hz), 7.48-7.66 (4H, m), 7.75 (1H, d, J=9Hz), 8.57 (1H, s), 8.63 (1H, d, J=8Hz), 8.72 (1H, s)

(9) 8-(2,6-Dichlorobenzoylamino)-4-(3-n-hexylureido)-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and n-hexylamine)
mp : 241-244°C
NMR (DMSO-d_6, δ) : 0.88 (3H, t, J=7Hz), 1.22-1.52 (8H, m), 2.33 (3H, s), 3.10 (2H, q, J=7Hz), 6.41 (1H, t, J=6Hz), 7.48-7.65 (4H, m), 7.74 (1H, d, J=8Hz), 8.57 (1H, s), 8.62 (1H, d, J=8Hz), 8.70 (1H, s)

(10) 4-[3-(Cyclopropylmethyl)ureido]-8-(2,6-dichlorobenzoylamino)-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and (aminomethyl)cyclopropane)
mp : 261°C
NMR (DMSO-d_6, δ) : 0.16-0.25 (2H, m), 0.39-0.49 (2H, m), 0.91-1.06 (1H, m), 2.33 (3H, s), 3.00 (2H, d, J=7Hz), 6.49 (1H, t, J=7Hz), 7.45-7.64 (4H, m), 7.75 (1H, d, J=9Hz), 8.59 (1H, br s), 8.61 (1H, d, J=9Hz), 8.70 (1H, s)

(11) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-(piperidinocarbonylamino)quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and piperidine)
mp : 223-226°C
NMR (DMSO-d_6, δ) : 1.50-1.73 (6H, m), 2.30 (3H, s), 3.47-3.57 (4H, m), 7.48-7.65 (4H, m), 7.73 (1H, d, J=8Hz), 8.63 (1H, d, J=8Hz), 8.70 (1H, s), 8.73 (1H, s), 10.69 (1H, s)

(12) 4-(3-Cyclohexylureido)-8-(2,6-dichlorobenzoylamino)-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and cyclohexylamine)
mp : 247-264°C
NMR (DMSO-d_6, δ) : 1.15-1.33 (5H, m), 1.53-1.58 (1H, m), 1.66-1.71 (2H, m), 1.82-1.86 (2H, m), 3.43-3.52 (1H, m), 6.39 (1H, d, J=7.5Hz), 7.48-7.63 (5H, m), 7.83 (1H, d, J=8.0Hz), 8.50 (1H, s), 8.63 (1H, d, J=8.0Hz), 8.71 (1H, s)

(13) 8-(2,6-Dichlorobenzoylamino)-4-[3-(2-methoxyethyl)-ureido]-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-

methylquinoline and 2-methoxyethylamine)
mp : 246-249°C
NMR ($CDCl_3$, δ) : 2.40 (3H, s), 3.35 (3H, s), 3.41-3.54 (4H, m), 5.22 (1H, t, J=5Hz), 7.28-7.42 (3H, m), 7.52 (1H, t, J=8Hz), 7.65 (1H, d, J=8Hz), 8.58 (1H, s), 8.87 (1H, d, J=8Hz)

(14) 4-[3,3-Bis(2-methoxyethyl)ureido]-8-(2,6-dichlorobenzoyl amino)-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and bis(2-methoxyethyl)amine)
mp : 169-175°C
NMR (DMSO-d_6, δ) : 2.29 (3H, s), 3.36 (6H, s), 3.50-3.69 (8H, m), 7.46-7.70 (5H, m), 8.53 (1H, br s), 8.63 (1H, d, J=9Hz), 8.71 (1H, s)

(15) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-(morpholinocarbonylamino)quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and morpholine)
mp : 227-231°C
NMR (DMSO-d_6, δ) : 2.32 (3H, s), 3.48-3.58 (4H, m), 3.62-3.72 (4H, m), 7.47-7.66 (5H, m), 7.75 (1H, d, J=8Hz), 8.63 (1H, d, J=8Hz), 8.75 (1H, s), 8.80 (1H, s), 10.71 (1H, s)

(16) 8-(2,6-Dichlorobenzoylamino)-4-[3-(ethoxycarbonylmethyl)ureido]-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and glycine ethyl ester hydrochloride)
mp : 243-245°C
NMR (DMSO-d_6, δ) : 1.21 (3H, t, J=8Hz), 2.37 (3H, s), 3.88 (2H, d, J=6Hz), 4.12 (2H, q, J=8Hz), 6.77 (1H, t, J=6Hz), 7.48-7.66 (4H, m), 7.77 (1H, d, J=8Hz), 8.62 (1H, d, J=8Hz), 8.73 (1H, s), 8.90 (1H, s)

(17) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[(4-methyl-1-piperazinyl)carbonylamino]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 1-methylpiperazine)
mp : 265.5-268°C
NMR (DMSO-d_6, δ) : 2.22 (3H, s), 2.30 (3H, s), 2.37 (4H, t, J=4.5Hz), 3.55 (4H, t, J=4.5Hz), 7.51 (1H, dd, J=8.5, 7.5Hz), 7.55-7.63 (3H, m), 7.73 (1H, d, J=7.5Hz), 8.62 (1H, d, J=7.5Hz), 8.73 (1H, s), 8.77 (1H, s)

(18) 4-[(4-Acetyl-1-piperazinyl)carbonylamino]-8-(2,6-dichlorobenzoylamino)-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 1-acetylpiperazine)
mp : 232-236°C
NMR (DMSO-d_6, δ) : 2.08 (3H, s), 2.32 (3H, s), 3.48-3.62 (8H, m), 7.48-7.66 (4H, m), 7.77 (1H, d, J=9Hz), 8.63 (1H, d, J=9Hz), 8.77 (1H, s), 8.88 (1H, s)

(19) 4-(3-Benzylureido)-8-(2,6-dichlorobenzoylamino)-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and benzylamine)
mp : 216-219°C
NMR (DMSO-d_6, δ) : 2.35 (3H, s), 4.33 (2H, d, J=6.0Hz), 7.10 (1H, dd, J=7.0, 7.0Hz), 7.22-7.29 (1H, m), 7.32-7.38 (4H, m), 7.50-7.65 (4H, m), 7.80 (1H, d, J=8.0Hz), 8.64 (1H, d, J=8.0Hz), 8.73 (1H, s), 8.90 (1H, br), 10.69 (1H, s)

(20) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(2-pyridylmethyl)ureido]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-

methylquinoline and 2-aminomethylpyridine)
mp : 246-251°C
NMR (DMSO-d_6, δ) : 2.36 (3H, s), 4.44 (2H, d, J=6Hz), 7.10 (1H, t, J=7Hz), 7.27 (1H, m), 7.37 (1H, d, J=9Hz), 7.46-7.66 (4H, m), 7.75-7.86 (2H, m), 8.53 (1H, m), 8.63 (1H, d, J=9Hz), 8.73 (1H, s), 8.94 (1H, br s)

(21) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(3-pyridylmethyl)ureido]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 3-aminomethylpyridine)
mp : 237-239°C
NMR (DMSO-d_6, δ) : 2.33 (3H, s), 4.36 (2H, d, J=6.0Hz), 7.01 (1H, t, J=6.0Hz), 7.39 (1H, dd, J=7.5, 4.5Hz), 7.49-7.61 (3H, m), 7.63 (1H, d, J=7.5Hz), 7.71-7.80 (2H, m), 8.47 (1H, d, J=4.5Hz), 8.54 (1H, d, J=1.0Hz), 8.63 (1H, d, J=7.5Hz), 8.73 (1H, s), 8.79 (1H, s)

(22) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(4-pyridylmethyl)ureido]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 4-aminomethylpyridine)
mp : 221-224°C
NMR (DMSO-d_6, δ) : 2.35 (3H, s), 4.36 (2H, d, J=6.0Hz), 7.06 (1H, t, J=6.0Hz), 7.31 (2H, d, J=4.5Hz), 7.47-7.61 (3H, m), 7.63 (1H, d, J=7.5Hz), 7.79 (1H, d, J=7.5Hz), 8.51 (2H, d, J=4.5Hz), 8.64 (1H, d, J=7.5Hz), 8.73 (1H, s), 8.89 (1H, s)

(23) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(thiazol-2-yl)ureido]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 2-aminothiazole)

mp : 152-156°C

NMR ($CDCl_3$, δ) : 2.38 (3H, s), 6.93 (1H, d, J=3Hz), 7.29-7.45 (4H, m), 7.52 (1H, t, J=8Hz), 7.60-7.68 (1H, br), 8.52 (1H, s), 8.86 (1H, d, J=8Hz), 9.98 (1H, s)

(24) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(5-methyl-1,3,4-thiadiazol-2-yl)ureido]quinoline

(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 2-amino-5-methyl-1,3,4-thiadiazole)

mp : 285-287°C

NMR (DMSO-d_6, δ) : 2.38 (3H, s), 2.55 (3H, s), 7.45-7.64 (4H, m), 7.77 (1H, d, J=9Hz), 8.65 (1H, d, J=9Hz), 8.81 (1H, s)

(25) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-(3-phenylureido)quinoline

(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and aniline)

mp : 206-207°C

NMR (DMSO-d_6, δ) : 2.40 (3H, s), 6.96 (1H, dd, J=7.0, 7.0Hz), 7.28 (2H, dd, J=7.0, 7.0Hz), 7.48-7.67 (7H, m), 7.87 (1H, d, J=8.0Hz), 8.64 (1H, d, J=8.0Hz), 8.76 (1H, s), 10.71 (1H, s)

(26) 4-[3-(4-Chlorophenyl)ureido]-8-(2,6-dichlorobenzoylamino)-3-methylquinoline

(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 4-chloroaniline)

mp : 274-277°C

NMR (DMSO-d_6, δ) : 2.39 (3H, s), 7.34 (2H, d, J=8.5Hz), 7.50-7.60 (1H, dd, J=8.0, 8.0Hz), 7.84 (1H, d, J=8.0Hz), 8.66 (1H, d, J=8.0Hz), 8.78 (1H, s), 8.91 (1H, s), 9.14 (1H, s), 10.73 (1H, s)

(27) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(4-nitrophenyl)ureido]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 4-nitroaniline)
mp : 240-243°C
NMR (DMSO-d_6, δ) : 2.42 (3H, s), 7.48-7.62 (4H, m), 7.67 (1H, t, J=8Hz), 7.73 (2H, d, J=9Hz), 7.84 (1H, d, J=8Hz), 8.22 (2H, d, J=9Hz), 8.68 (1H, d, J=8Hz), 8.81 (1H, s), 9.12 (1H, s), 9.77 (1H, s)

(28) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(3-pyridyl)-ureido]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 3-aminopyridine)
mp : 217-220°C
NMR (DMSO-d_6, δ) : 2.40 (3H, s), 7.31 (1H, dd, J=5, 8Hz), 7.49-7.69 (4H, m), 7.83 (1H, d, J=8Hz), 7.97 (1H, d, J=8Hz), 8.20 (1H, d, J=5Hz), 8.62-8.69 (2H, m), 8.97 (1H, s), 9.00 (1H, s), 9.18 (1H, s)

(29) 8-(2,6-Dichlorobenzoylamino)-4-[3-(4,6-dichloropyrimidin-5-yl)ureido]-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 5-amino-4,6-dichloropyrimidine)
mp : 247-249°C
NMR (DMSO-d_6, δ) : 2.44 (3H, s), 7.47-7.60 (3H, m), 7.70 (1H, dd, J=8.0, 8.0Hz), 7.87 (1H, d, J=8.0Hz), 8.64 (1H, d, J=8.0Hz), 8.79 (1H, s), 8.83 (1H, s), 9.17 (1H, br), 9.40 (1H, br), 10.74 (1H, s)

(30) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(8-quinolyl)-ureido]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 8-aminoquinoline)
mp : 262-265°C

NMR (DMSO-d_6, δ) : 2.44 (3H, s), 7.50-7.63 (6H, m), 7.65-7.71 (2H, m), 7.90 (1H, d, J=8.0Hz), 8.43 (1H, d, J=8.0Hz), 8.54 (1H, d, J=7.5Hz), 8.82 (1H, s), 8.99 (1H, d, J=5.0Hz)

(31) 4-[3-(1H-Benzimidazol-2-yl)ureido]-8-(2,6-dichlorobenzoylamino)-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 2-amino-1H-benzimidazole)
mp : 170-176°C
NMR (DMSO-d_6, δ) : 2.44 (3H, s), 7.00-7.11 (2H, m), 7.30-7.42 (2H, m), 7.48-7.60 (3H, m), 7.65 (1H, t, J=9Hz), 7.84 (1H, d, J=9Hz), 8.66 (1H, d, J=9Hz), 8.82 (1H, s)

(32) 8-(2,6-Dichlorobenzoylamino)-4-[3-(dimethylamino)-ureido]-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 1,1-dimethylhydrazine)
mp : 248°C
NMR (DMSO-d_6, δ) : 2.36 (3H, s), 2.64 (6H, s), 7.45-7.64 (4H, m), 7.70 (1H, d, J=9Hz), 7.77 (1H, br s), 8.60 (1H, d, J=9Hz), 8.75 (1H, s), 8.90 (1H, br s)

(33) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-(3-morpholinoureido)quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 4-aminomorpholine)
mp : 263-267°C
NMR (DMSO-d_6, δ) : 2.35 (3H, s), 3.18-3.24 (2H, m), 3.31-3.39 (2H, m), 3.63-3.78 (4H, br), 7.46-7.60 (4H, m), 7.67-7.71 (1H, m), 7.93 (1H, s), 8.60 (1H, d, J=8.0Hz), 8.75 (1H, s), 8.92 (1H, s)

(34) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(5-

methylisoxazol-3-yl)ureido]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 3-amino-5-methylisoxazole)
mp : 153-156°C
NMR (DMSO-d_6, δ) : 2.37 (3H, s), 2.39 (3H, s), 4.32-4.38 (1H, br), 6.49 (1H, s), 7.48-7.60 (3H, m), 7.67 (1H, t, J=8Hz), 7.78 (1H, d, J=8Hz), 8.67 (1H, d, J=8Hz), 8.79 (1H, s)

(35) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-ureidoquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 7N solution of ammonia in methanol)
mp : 228-230°C
NMR (DMSO-d_6, δ) : 2.35 (3H, s), 6.12 (2H, br s), 7.52 (1H, dd, J=9.0, 7.0Hz), 7.55-7.61 (2H, m), 7.63 (1H, t, J=7.5Hz), 7.78 (1H, d, J=7.5Hz), 8.63 (1H, d, J=7.5Hz), 8.67 (1H, s), 8.72 (1H, s)

(36) 4-(3-Cyclopropylureido)-8-(2,6-dichlorobenzoylamino)-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and cyclopropylamine)
mp : 289-290°C
NMR (DMSO-d_6, δ) : 0.48-0.53 (2H, m), 0.65-0.71 (2H, m), 2.35 (3H, s), 2.58-2.64 (1H, m), 6.70 (1H, br), 7.49-7.65 (4H, m), 7.75 (1H, d, J=8.0Hz), 8.52 (1H, s), 8.63 (1H, d, J=8.0Hz), 8.73 (1H, s), 10.71 (1H, s)

(37) (±)-4-(3-sec-Butylureido)-8-(2,6-dichlorobenzoylamino)-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and (±)-sec-butylamine)
mp : 284-290°C (dec.)
NMR (DMSO-d_6, δ) : 0.91 (3H, t, J=7Hz), 1.11 (3H, d,

J=7Hz), 1.46 (2H, dq, J=7, 7Hz), 2.33 (3H, s), 3.62 (1H, ddq, J=8, 7, 7Hz), 6.28 (1H, d, J=8Hz), 7.48-7.65 (4H, m), 7.75 (4H, m), 8.48 (1H, s), 8.63 (1H, d, J=8Hz), 8.71 (1H, s), 10.69 (1H, s)

(38) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(2-methylpropyl)ureido]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 2-methylpropylamine)
mp : 235-238°C
NMR (DMSO-d_6, δ) : 0.90 (6H, d, J=7Hz), 1.24 (1H, hept., J=7Hz), 2.34 (3H, s), 2.96 (2H, t, J=7Hz), 6.48 (1H, t, J=7Hz), 7.46-7.67 (4H, m), 7.75 (1H, d, J=9Hz), 8.56 (1H, s), 8.63 (1H, d, J=9Hz), 8.72 (1H, s)

(39) 4-(3-tert-Butylureido)-8-(2,6-dichlorobenzoylamino)-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and tert-butylamine)
mp : >300°C
NMR (DMSO-d_6, δ) : 1.34 (9H, s), 2.34 (3H, s), 6.33 (1H, s), 7.48-7.64 (4H, m), 7.75 (1H, d, J=8.0Hz), 8.43 (1H, s), 8.63 (1H, d, J=8.0Hz), 8.70 (1H, s), 10.70 (1H, s)

(40) 4-(3-Cyclopentylureido)-8-(2,6-dichlorobenzoylamino)-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and cyclopentylamine)
mp : 248-249°C
NMR (DMSO-d_6, δ) : 1.37-1.73 (6H, m), 1.81-1.93 (2H, m), 2.35 (3H, s), 3.97 (1H, m), 6.48 (1H, d, J=7.5Hz), 7.52 (1H, dd, J=9.0, 7.0Hz), 7.56-7.66 (3H, m), 7.75 (1H, d, J=7.5Hz), 8.44 (1H, s), 8.63

(1H, d, J=7.5Hz), 8.70 (1H, s)

(41) 8-(2,6-Dichlorobenzoylamino)-4-[3-(1-ethylpropyl)-ureido]-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 1-ethylpropylamine)
mp : 244-245°C
NMR (DMSO-d_6, δ) : 0.91 (6H, t, J=7.5Hz), 1.31-1.58 (4H, m), 2.34 (3H, s), 3.49 (1H, m), 6.22 (1H, d, J=7.5Hz), 7.52 (1H, dd, J=9.0, 7.0Hz), 7.55-7.60 (2H, m), 7.62 (1H, t, J=7.5Hz), 7.76 (1H, d, J=7.5Hz), 8.49 (1H, s), 8.63 (1H, d, J=7.5Hz), 8.71 (1H, s)

(42) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-(3-neopentylureido)quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and neopentylamine)
mp : 264-265°C
NMR (DMSO-d_6, δ) : 0.91 (9H, s), 2.34 (3H, s), 2.97 (2H, d, J=7Hz), 6.52 (1H, t, J=7Hz), 7.48-7.67 (4H, m), 7.77 (1H, d, J=8Hz), 8.59 (1H, s), 8.64 (1H, d, J=8Hz), 8.72 (1H, s)

(43) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(2-piperidinoethyl)ureido]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and N-(2-aminoethyl)piperidine)
mp : 190-194°C
NMR (DMSO-d_6, δ) : 1.37-1.58 (6H, m), 2.33 (3H, s), 2.34-2.46 (6H, m), 3.18-3.28 (2H, m), 6.36 (1H, t, J=7Hz), 7.48-7.65 (4H, m), 7.77 (1H, d, J=8Hz), 8.63 (1H, d, J=8Hz), 8.71 (1H, s), 8.77-8.83 (1H, br)

(44) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(2,2,3,3,3-pentafluoropropyl)ureido]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 2,2,3,3,3-pentafluoropropylamine)
mp : 243-244°C
NMR (DMSO-d_6, δ) : 2.35 (3H, s), 3.95-4.10 (2H, m), 7.05 (1H, t, J=7.0Hz), 7.52 (1H, dd, J=8.5, 7.5Hz), 7.58 (1H, d, J=8.5Hz), 7.59 (1H, t, J=7.5Hz), 7.65 (1H, d, J=7.5Hz), 7.71 (1H, d, J=7.5Hz), 8.65 (1H, d, J=7.5Hz), 8.76 (1H, s), 8.90 (1H, s)

(45) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(2,2,2-trifluoroethyl)ureido]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 2,2,2-trifluoroethylamine)
mp : 295°C (dec.)
NMR (DMSO-d_6, δ) : 2.34 (3H, s), 3.85-4.03 (2H, m), 7.08 (1H, br t, J=7Hz), 7.46-7.65 (4H, m), 7.73 (1H, d, J=9Hz), 8.65 (1H, d, J=9Hz), 8.76 (1H, s), 8.90 (1H, br s)

(46) (±)-8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(tetrahydrofuran-2-on-3-yl)ureido]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and (±)-α-amino-γ-butyrolactone hydrobromide)
mp : 172-176°C
NMR ($CDCl_3$, δ) : 1.84 (1H, m), 2.05-2.27 (1H, m), 2.40 (3H, s), 3.94-4.10 (2H, m), 4.48-4.57 (1H, m), 6.30 (1H, d, J=3.0Hz), 7.32-7.43 (4H, m), 7.60-7.68 (1H, m), 8.76 (1H, s), 8.95 (1H, d, J=8.0Hz), 10.24 (1H, s)

(47) (±)-8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(pyrrolidin-3-yl)ureido]quinoline

(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and (±)-3-aminopyrrolidine)

mp : 216-218°C

NMR ($CDCl_3$, δ) : 1.17-1.25 (1H, m), 1.90 (1H, br), 2.40 (3H, s), 3.35-3.40 (1H, m), 3.56-3.63 (1H, m), 3.76 (3H, br), 7.30-7.42 (3H, m), 7.58 (1H, dd, J=8.0, 8.0Hz), 7.73 (1H, d, J=8.0Hz), 8.60 (1H, s), 8.85 (1H, d, J=8.0Hz)

(48) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(pyridin-2-yl)ureido]quinoline

(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 2-aminopyridine)

mp : 234-235°C

NMR (DMSO-d_6, δ) : 2.41 (3H, s), 7.03 (1H, t, J=6.0Hz), 7.48-7.61 (4H, m), 7.64 (1H, d, J=8.0Hz), 7.76 (1H, t, J=8.0Hz), 7.81 (1H, d, J=8.0Hz), 8.30 (1H, d, J=6.0Hz), 8.67 (1H, d, J=8.0Hz), 8.78 (1H, s), 10.73 (1H, s)

(49) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(4-methyloxazol-2-yl)ureido]quinoline

(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 2-amino-4-methyloxazole)

mp : 154-160°C

NMR (DMSO-d_6, δ) : 2.09 (3H, s), 2.40 (3H, s), 7.68 (1H, t, J=8Hz), 7.48-7.62 (4H, m), 7.78 (1H, d, J=8Hz), 8.68 (1H, d, J=8Hz), 8.82 (1H, s)

(50) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(3-methylisothiazol-5-yl)ureido]quinoline

(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 5-amino-3-methylisothiazole hydrochloride)

mp : 190-192°C

NMR (DMSO-d_6, δ) : 2.28 (3H, s), 2.38 (3H, s), 6.67 (1H, s), 7.49-7.69 (4H, m), 7.78 (1H, d, J=8Hz), 8.68 (1H, d, J=8Hz), 8.83 (1H, s)

(51) 8-(2,6-Dichlorobenzoylamino)-4-[3-(4-methoxyphenyl)-ureido]-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 4-methoxyaniline)
mp : 286-289°C
NMR (DMSO-d_6, δ) : 2.40 (3H, s), 3.72 (3H, s), 6.87 (2H, d, J=9.0Hz), 7.40 (2H, d, J=9.0Hz), 7.50-7.66 (4H, m), 7.88 (1H, d, J=8.0Hz), 8.65 (1H, d, J=8.0Hz), 8.76 (1H, s), 9.17 (1H, s), 9.26 (1H, s), 10.73 (1H, s)

(52) 8-(2,6-Dichlorobenzoylamino)-4-(3-phenylureido)quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)quinoline and aniline)
mp : 165-166°C
NMR (DMSO-d_6, δ) : 7.07 (1H, t, J=8Hz), 7.32-7.40 (2H, m), 7.50-7.66 (5H, m), 7.73 (1H, t, J=8Hz), 8.02 (1H, d, J=8Hz), 8.37 (1H, d, J=5Hz), 8.71 (1H, d, J=5Hz), 8.78 (1H, d, J=8Hz), 9.38 (1H, s), 9.44 (1H, s)

(53) 4-[3-(3-Chlorophenyl)ureido]-8-(2,6-dichlorobenzoylamino)-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 3-chloroaniline)
mp : 279-282°C
NMR (DMSO-d_6, δ) : 2.42 (3H, s), 7.03-7.05 (1H, m), 7.30-7.34 (2H, m), 7.50-7.68 (5H, m), 7.83 (1H, d, J=8.0Hz), 8.66 (1H, d, J=8.0Hz), 8.79 (1H, s), 8.97 (1H, s), 9.20 (1H, s), 10.76 (1H, s)

(54) 8-(2,6-Dichlorobenzoylamino)-4-[3-(2-methoxycarbonylthiophen-3-yl)ureido]-3-methylquinoline (from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methyl-quinoline and methyl 3-amino-2-thiophenecarboxylate)

mp : 237-240°C

NMR (DMSO-d_6, δ) : 2.40 (3H, s), 3.87 (3H, s), 7.50-7.60 (3H, m), 7.65 (1H, dd, J=8.0, 8.0Hz), 7.81-7.88 (2H, m), 7.95 (1H, d, J=6.0Hz), 8.67 (1H, d, J=8.0Hz), 8.80 (1H, s), 9.90 (1H, s), 10.17 (1H, s), 10.76 (1H, s)

(55) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(3-trifluoromethylphenyl)ureido]quinoline (from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 3-trifluoromethylaniline)

mp : 233-235°C

NMR (DMSO-d_6, δ) : 2.42 (3H, s), 7.33 (1H, d, J=8Hz), 7.49-7.70 (6H, m), 7.84 (1H, d, J=8Hz), 8.01 (1H, s), 8.68 (1H, d, J=8Hz), 8.81 (1H, s), 9.00 (1H, s), 9.36 (1H, s)

(56) 8-(2,6-Dichlorobenzoylamino)-4-[3-(3-fluorophenyl)-ureido]-3-methylquinoline (from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 3-fluoroaniline)

mp : 275-283°C

NMR (DMSO-d_6, δ) : 2.40 (3H, s), 6.80 (1H, m), 7.19 (1H, d, J=8Hz), 7.33 (1H, m), 7.45-7.70 (5H, m), 7.83 (1H, d, J=8Hz), 8.65 (1H, d, J=8Hz), 8.79 (1H, s), 8.93 (1H, s), 9.22 (1H, s), 10.75 (1H, s)

(57) 4-[3-(3-Bromophenyl)ureido]-8-(2,6-dichlorobenzoylamino)-3-methylquinoline (from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 3-bromoaniline)

mp : 271-274°C
NMR ($DMSO-d_6$, δ) : 2.40 (3H, s), 7.17 (1H, d, J=8Hz), 7.25 (1H, dd, J=8, 8Hz), 7.38 (1H, d, J=8Hz), 7.49-7.70 (4H, m), 7.79-7.89 (2H, m), 8.65 (1H, d, J=8Hz), 8.79 (1H, s), 8.95 (1H, s), 9.17 (1H, s), 10.75 (1H, s)

(58) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[3-(3-methylphenyl)ureido]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and 3-methylaniline)
mp : 230-231°C
NMR ($DMSO-d_6$, δ) : 2.29 (3H, s), 2.42 (3H, s), 6.81 (1H, d, J=7.5Hz), 7.17 (1H, t, J=7.5Hz), 7.27 (1H, d, J=7.5Hz), 7.34 (1H, s), 7.52 (1H, dd, J=8.5, 7.0Hz), 7.56-7.61 (2H, m), 7.65 (1H, t, J=7.5Hz), 7.83 (1H, d, J=7.5Hz), 8.67 (1H, d, J=7.5Hz), 8.79 (1H, s), 8.86 (1H, s), 8.91 (1H, s)

(59) 8-(2,6-Dichlorobenzoylamino)-4-[3-(3-ethoxycarbonylphenyl)ureido]-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and ethyl 3-aminobenzoate)
mp : 250-251°C
NMR ($DMSO-d_6$, δ) : 1.31 (3H, t, J=7.0Hz), 2.42 (3H, s), 4.31 (2H, q, J=7.0Hz), 7.44 (1H, t, J=7.5Hz), 7.53 (1H, dd, J=8.5, 7.0Hz), 7.56-7.63 (3H, m), 7.65 (1H, t, J=7.5Hz), 7.72 (1H, d, J=7.5Hz), 7.84 (1H, d, J=7.5Hz), 8.19 (1H, s), 8.68 (1H, d, J=7.5Hz), 8.80 (1H, s), 8.91 (1H, s), 9.27 (1H, s)

(60) 4-[3-(2-Chlorophenyl)ureido]-8-(2,6-dichlorobenzoylamino)-3-methylquinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-

methylquinoline and 2-chloroaniline)

mp : 275-278°C

NMR (DMSO-d_6, δ) : 2.43 (3H, s), 7.06 (1H, dd, J=7.0, 7.0Hz), 7.30 (1H, dd, J=7.0, 7.0Hz), 7.50-7.60 (4H, m), 7.68 (1H, dd , J=7.0, 7.0Hz), 7.84 (1H, d, J=7.0Hz), 8.17 (1H, d, J=7.0Hz), 8.65-8.70 (2H, m), 8.80 (1H, s), 9.56 (1H, s), 10.70 (1H, s)

(61) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-(3-methyl-3-phenylureido)quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and N-methylaniline)

mp : 212-219°C

NMR (DMSO-d_6, δ) : 2.35 (3H, s), 2.50 (3H, s), 7.30 (1H, m), 7.42-7.65 (7H, m), 7.74 (1H, d, J=8Hz), 8.30 (1H, s), 8.62 (1H, d, J=8Hz), 8.75 (1H, s), 10.69 (1H, s)

(62) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[(thiomorpholin-4-yl)carbonylamino]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquionline and thiomorpholine)

mp : 249-251°C

NMR (DMSO-d_6, δ) : 2.32 (3H, s), 2.64-2.72 (4H, br s), 3.79-3.88 (4H, br s), 7.48-7.66 (4H, m), 7.85 (1H, d, J=8Hz), 8.63 (1H, d, J=8Hz), 8.76 (1H, s), 8.81 (1H, s)

(63) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-[(pyrrolidin-1-yl)carbonylamino]quinoline
(from 4-amino-8-(2,6-dichlorobenzoylamino)-3-methylquinoline and pyrrolidine)

mp : 236-245°C

NMR (DMSO-d_6, δ) : 1.84-2.00 (4H, m), 2.34 (3H, s), 3.37-3.54 (4H, m), 7.46-7.65 (4H, m), 7.79 (1H, d,

J=9Hz), 8.42 (1H, br s), 8.62 (1H, d, J=9Hz), 8.74 (1H, s)

(64) 8-[(2,4-Dichloropyridin-3-yl)carbonylamino]-3-methyl-4-(piperidinocarbonylamino)quinoline
(from 4-amino-8-[(2,4-dichloropyridin-3-yl)carbonylamino]-3-methylquinoline and piperidine)
mp : 215-216°C
NMR (DMSO-d_6, δ) : 1.51-1.69 (6H, m), 2.32 (3H, s), 3.48-3.56 (4H, m), 7.60 (1H, t, J=7.5Hz), 7.73 (1H, d, J=6.0Hz), 7.74 (1H, d, J=7.5Hz), 8.48 (1H, d, J=6.0Hz), 8.65 (1H, d, J=7.5Hz), 8.69 (1H, s), 8.77 (1H, s)

(65) 8-[(2,4-Dichloropyridin-3-yl)carbonylamino]-4-(3-ethyl-3-methylureido)-3-methylquinoline
(from 4-amino-8-[(2,4-dichloropyridin-3-yl)carbonylamino]-3-methylquinoline and N-ethyl-N-methylamine)
mp : 214-215.5°C
NMR (DMSO-d_6, δ) : 1.16 (3H, t, J=7.5Hz), 2.31 (3H, s), 3.02 (3H, s), 3.43 (2H, q, J=7.5Hz), 7.60 (1H, t, J=7.5Hz), 7.73 (1H, d, J=6.0Hz), 7.74 (1H, d, J=7.5Hz), 8.47 (1H, d, J=6.0Hz), 8.53 (1H, s), 8.65 (1H, d, J=7.5Hz), 8.76 (1H, s)

Example 5

(1) To a solution of 1,4-dihydro-3-methyl-8-nitro-4-oxoquinoline (3.29 g) in acetonitrile (35 ml) was added p-toluenesulfonyl isocyanate (9.53 g) at ambient temperature, and the mixture was refluxed for 3 hours. The solvent was removed in vacuo, and the residue was diluted with ethanol (10 ml). The solid was collected by filtration under reduced pressure and washed with ethanol (20 ml) to afford 3-methyl-8-nitro-4-(4-toluenesulfonamido)quinoline (3.49 g) as a brown crystal.

NMR ($DMSO-d_6$, δ) : 2.07 (3H, s), 2.38 (3H, s), 7.37 (2H, d, J=9Hz), 7.53 (2H, d, J=9Hz), 7.61 (1H, t, J=8Hz), 8.12 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz), 8.88 (1H, s)

(2) 97% Sulfuric acid (57 ml) was cooled to 5°C, and 3-methyl-8-nitro-4-(4-toluenesulfonamido)quinoline (7.6 g) was added portionwise thereto over a period of 10 minutes in an ice bath. The resulting mixture was stirred at 0°C for 1 hour and at ambient temperature for 1 hour. The reaction mixture was added dropwise to ice (100 g) over a period of 30 minutes with stirring at 5-15°C. To the mixture was added 10N-sodium hydroxide aqueous solution (ca. 220 ml) over a period of 1 hour with stirring at 5-30°C (final pH = 10-12). The mixture was stirred at ambient temperature for 1 hour, and the precipitate was collected in vacuo. The yellow solid was washed with hot ethanol (500 ml) to give 4-amino-3-methyl-8-nitroquinoline (4.56 g) as a yellow solid.

mp : 262-263.5°C

NMR ($DMSO-d_6$, δ) : 2.21 (3H, s), 6.87 (2H, br s), 7.47 (1H, t, J=7.5Hz), 7.97 (1H, d, J=7.5Hz), 8.31 (1H, s), 8.47 (1H, d, J=7.5Hz)

(3) To a mixture of 4-amino-3-methyl-8-nitroquinoline (100 mg), 1,8-diazabicyclo[5.4.0]undec-7-ene (89.9 mg) and N,N-dimethylformamide (1 ml) was added 1,1'-carbonyldiimidazole (95.8 mg) under nitrogen atmosphere, and the mixture was stirred for 2 hours at ambient temperature. To the mixture was added 2M solution of methylamine in tetrahydrofuran (0.37 ml) at 0°C, and the mixture was stirred for 15 hours at ambient temperature. Water was added thereto at 0°C, and the resulting precipitates were collected by filtration and washed with ethanol to give 3-methyl-4-(3-methylureido)-8-nitroquinoline (68.1 mg) as off-white solid.

mp : 222.5-223°C

NMR ($DMSO-d_6$, δ) : 2.35 (3H, s), 2.69 (3H, d, J=4.0Hz), 6.42 (1H, q, J=4.0Hz), 7.69 (1H, t, J=7.5Hz), 8.15 (1H, d, J=7.5Hz), 8.18 (1H, d, J=7.5Hz), 8.77 (1H, s), 8.55 (1H, s)

(4) To a mixture of 3-methyl-4-(3-methylureido)-8-nitroquinoline (683 mg) and ammonium chloride (98.3 mg) in water (2 ml) and ethanol (13 ml) was added iron (733 mg) at ambient temperature, and the mixture was refluxed for 1.5 hours. After cooled to ambient temperature, insoluble material was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (methanol:chloroform = 1:10, v/v) and washed with acetonitrile to give 8-amino-3-methyl-4-(3-methylureido)quinoline (277 mg) off-white solid.

mp : 237-240°C

NMR ($DMSO-d_6$, δ) : 2.28 (3H, s), 2.66 (3H, d, J=4.5Hz), 5.84 (2H, s), 6.20 (1H, q, J=4.5Hz), 6.77 (1H, d, J=7.5Hz), 7.07 (1H, d, J=7.5Hz), 7.23 (1H, t, J=7.5Hz), 8.34 (1H, s), 8.54 (1H, s)

(5) To 2,4-dichloropyridine-3-carboxylic acid (99.2 mg) was added thionyl chloride (1.02 ml), and N,N-dimethylformamide (1 drop) was added thereto. The mixture was stirred at 70°C for 1 hour, and the reaction mixture was concentrated in vacuo. The residue was suspended in ethylene chloride (1 ml) and triethylamine (0.154 ml), and to the mixture was added 8-amino-3-methyl-4-(3-methylureido)quinoline (85 mg) at 0°C under nitrogen atmosphere. The mixture was stirred at 70°C for 1.5 hours and cooled to ambient temperature. The reaction mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate solution, water and brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (methanol:chloroform = 1:10, v/v) and washed with

acetonitrile to give 8-[(2,4-dichloropyridin-3-yl)carbonylamino]-3-methyl-4-(3-methylureido)quinoline (84.9 mg) off-white solid.

mp : 243-245°C

NMR (DMSO-d_6, δ) : 2.33 (3H, s), 2.68 (3H, d, J=4.5Hz), 6.32 (1H, q, J=4.5Hz), 7.61 (1H, t, J=7.5Hz), 7.73 (1H, d, J=6.0Hz), 7.77 (1H, d, J=7.5Hz), 8.47 (1H, d, J=6.0Hz), 8.64 (1H, s), 8.65 (1H, d, J=7.5Hz), 8.73 (1H, s)

Example 6

The following compounds were obtained according to a similar manner to that of Example 5-(5).

(1) 3-Methyl-4-(3-methylureido)-8-[(4-trifluoromethyl-pyridin-3-yl)carbonylamino]quinoline
(from 8-amino-3-methyl-4-(3-methylureido)quinoline and 4-trifluoromethylpyridine-3-carboxylic acid)

mp : 279.5-282°C

NMR (DMSO-d_6, δ) : 2.33 (3H, s), 2.68 (3H, d, J=4.5Hz), 6.33 (1H, q, J=4.5Hz), 7.61 (1H, t, J=7.5Hz), 7.77 (1H, d, J=7.5Hz), 7.89 (1H, d, J=6.0Hz), 8.60 (1H, d, J=7.5Hz), 8.65 (1H, s), 8.73 (1H, s), 8.98 (1H, d, J=6.0Hz), 9.06 (1H, s)

(2) 8-[(2,4-Dimethylpyridin-3-yl)carbonylamino]-3-methyl-4-(3-methylureido)quinoline
(from 8-amino-3-methyl-4-(3-methylureido)quinoline and 2,4-dimethylpyridine-3-carboxylic acid)

mp : 199-201°C

NMR (DMSO-d_6, δ) : 2.32 (6H, s), 2.50 (3H, s), 2.68 (3H, d, J=5.5Hz), 6.32 (1H, q, J=5.5Hz), 7.21 (1H, d, J=5.5Hz), 7.61 (1H, t, J=7.5Hz), 7.77 (1H, d, J=7.5Hz), 8.40 (1H, d, J=5.5Hz), 8.57 (1H, d, J=7.5Hz), 8.65 (1H, s), 8.70 (1H, s)

(3) 8-[(2,4-Dichloropyridin-3-yl)carbonylamino]-4-(1,3-dimethylureido)-3-methylquinoline
(from 8-amino-4-(1,3-dimethylureido)-3-methylquinoline and 2,4-dichloropyridine-3-carboxylic acid)
mp : 154-161°C
NMR (DMSO-d_6, δ) : 2.32 (3H, s), 2.50 (3H, d, J=4.5Hz), 3.15 (3H, s), 7.52 (1H, d, J=8.0Hz), 7.67 (1H, dd, J=8.0, 8.0Hz), 7.73 (1H, d, J=6.0Hz), 8.48 (1H, d, J=6.0Hz), 8.71 (1H, d, J=8.0Hz), 8.86 (1H, s), 11.27 (1H, s)

(4) 8-[(2,4-Dichloropyridin-3-yl)carbonylamino]-3-methyl-4-(1,3,3-trimethylureido)quinoline
(from 8-amino-3-methyl-4-(1,3,3-trimethylureido)-quinoline and 2,4-dichloropyridine-3-carboxylic acid)
mp : 219-221°C
NMR (DMSO-d_6, δ) : 2.30 (3H, s), 2.47 (2x3H, s), 3.08 (3H, s), 7.67-7.77 (3H, m), 8.48 (1H, d, J=7Hz), 8.71 (1H, m), 8.82 (1H, s), 11.19 (1H, s)

(5) 3-Methyl-4-(1-methyl-3-phenylureido)-8-[(4-trifluoromethylpyridin-3-yl)carbonylamino]quinoline
(from 8-amino-3-methyl-4-(1-methyl-3-phenylureido)-quinoline and 4-trifluoromethylpyridine-3-carboxylic acid)
mp : 106-109°C
NMR ($CDCl_3$, δ) : 2.37 (3H, s), 2.50 (3H, s), 5.78 (1H, br s), 6.97-7.05 (1H, m), 7.14-7.27 (4H, m), 7.64-7.76 (3H, m), 8.78 (1H, s), 8.92 (1H, d, J=5.5Hz), 8.98 (1H, d, J=5.5Hz), 9.11 (1H, s)

<u>Example 7</u>

(1) 4-(3,3-Dimethylureido)-3-methyl-8-nitroquinoline was obtained from 4-amino-3-methyl-8-nitroquinoline, 2M solution of dimethylamine in tetrahydrofuran and

1,1'-carbonyldiimidazole according to a similar manner to that of Example 5-(3).

NMR (DMSO-d_6, δ) : 2.32 (3H, s), 2.99 (6H, s), 7.68 (1H, t, J=8Hz), 8.12 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz), 8.63 (1H, s), 8.86 (1H, s)

(2) 8-Amino-4-(3,3-dimethylureido)-3-methylquinoline was obtained according to a similar manner to that of Example 5-(4).

NMR (DMSO-d_6, δ) : 2.23 (3H, s), 2.98 (6H, s), 5.82 (2H, s), 6.77 (1H, d, J=8Hz), 7.06 (1H, d, J=8Hz), 7.21 (1H, t, J=8Hz), 8.29 (1H, s), 8.56 (1H, s)

(3) A solution of 8-amino-4-(3,3-dimethylureido)-3-methylquinoline (100 mg), 4-trifluoromethylpyridine-3-carboxylic acid (93.9 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (118 mg) and 1-hydroxybenzotriazole (83 mg) in N,N-dimethylformamide (4.0 ml) was stirred for 18 hours at ambient temperature. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (methanol-chloroform). The residue was crystallized from ethanol and diisopropyl ether to give 4-(3,3-dimethylureido)-3-methyl-8-[(4-trifluoromethylpyridin-3-yl)carbonylamino]quinoline (78 mg).

mp : 158-162°C

NMR (DMSO-d_6, δ) : 2.32 (3H, s), 3.03 (6H, s), 7.60 (1H, t, J=8Hz), 7.78 (1H, d, J=8Hz), 7.90 (1H, d, J=5Hz), 8.52-8.58 (1H, br), 8.60 (1H, d, J=8Hz), 8.77 (1H, s), 8.99 (1H, d, J=5Hz), 9.07 (1H, s)

Example 8

(1) To a suspension of 4-amino-3-methyl-8-nitroquinoline (800 mg) in toluene (12 ml) was added phenyl isocyanate (516

mg), and the reaction mixture was stirred for 12 hours at 90°C. The mixture was allowed to cool to ambient temperature and concentrated in vacuo. The residue was triturated with hot ethyl acetate to give 3-methyl-8-nitro-4-(3-phenylureido)quinoline as a white crystal (1.1 g).

mp : 251-254°C

NMR (DMSO-d_6, δ) : 2.44 (3H, s), 6.98 (1H, dd, J=8.0, 8.0Hz), 7.30 (2H, dd, J=8.0, 8.0Hz), 7.49 (2H, d, J=8.0Hz), 7.74 (1H, dd, J=8.0, 8.0Hz), 8.18 (1H, d, J=8.0Hz), 8.28 (1H, d, J=8.0Hz), 8.91 (1H, s), 8.97 (1H, s), 9.08 (1H, s)

(2) A stirred suspension of 3-methyl-8-nitro-4-(3-phenylureido)quinoline (98 mg) in ethanol (2 ml) was treated with platinum oxide catalyst (10 mg). Hydrogen atmosphere was introduced by using a hydrogen-filled balloon. After 1 hour of vigorous stirring the reaction mixture was filtered, and the filtrate was concentrated in vacuo followed by flash column chromatography on silica gel (1% methanol-chloroform). The crystalline product was triturated with hot ethanol to give 8-amino-3-methyl-4-(3-phenylureido)quinoline as an off-white crystal (66 mg).

mp : 222-224°C

NMR (DMSO-d_6, δ) : 2.35 (3H, s), 5.91 (2H, s), 6.80 (1H, d, J=8.0Hz), 6.97 (1H, dd, J=8.0, 8.0Hz), 7.13 (1H, d, J=8.0Hz), 7.24 (2H, d, J=8.0Hz), 7.28 (1H, dd, J=8.0, 8.0Hz), 7.47 (2H, d, J=8.0Hz), 8.57 (1H, s), 8.60 (1H, s), 8.91 (1H, s)

(3) 8-[(2,4-Dichloropyridin-3-yl)carbonylamino]-4-(3-phenylureido)-3-methylquinoline was obtained from 8-amino-3-methyl-4-(3-phenylureido)quinoline and 2,4-dichloropyridine-3-carboxylic acid according to a similar manner to that of Example 5-(5).

mp : >300°C

NMR ($DMSO-d_6$, δ) : 2.40 (3H, s), 6.99 (1H, dd, J=8.0, 8.0Hz), 7.29 (2H, dd, J=8.0, 8.0Hz), 7.49 (2H, d, J=8.0Hz), 7.66 (2H, d, J=8.0Hz), 7.74 (1H, d, J=4.5Hz), 7.86 (1H, d, J=8.0Hz), 8.48 (1H, d, J=4.5Hz), 8.68 (1H, d, J=8.0Hz), 8.80 (2H, s), 8.86 (1H, s), 8.98 (1H, s), 11.22 (1H, s)

Example 9

(1) To a solution of 3-methyl-8-nitro-4-(4-toluenesulfonamido)quinoline (3 g) in N,N-dimethylformamide (20 ml) was added potassium carbonate (5.8 g), and the reaction mixture was stirred at ambient temperature for 1 hour. To the mixture was added methyl iodide (2.38 g), and the mixture was stirred at ambient temperature for 30 minutes. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was triturated with ethanol to give 3-methyl-4-[N-methyl-N-(4-toluenesulfonyl)-amino]-8-nitroquinoline as a white crystal (2.96 g).

mp : 152-153°C

NMR ($DMSO-d_6$, δ) : 2.17 (3H, s), 2.44 (3H, s), 3.28 (3H, s), 7.47 (2H, d, J=7.5Hz), 7.68 (1H, dd, J=8.0, 8.0Hz), 7.71 (2H, d, J=7.5Hz), 7.83 (1H, d, J=8.0Hz), 8.22 (1H, d, J=8.0Hz), 9.00 (1H, s)

(2) 3-Methyl-4-methylamino-8-nitroquinoline was obtained according to a similar manner to that of Example 5-(2).

mp : 190-191°C

NMR ($DMSO-d_6$, δ) : 2.40 (3H, s), 3.26 (3H, d, J=6.0Hz), 6.58 (1H, q, J=6.0Hz), 7.47 (1H, dd, J=8.0, 8.0Hz), 7.96 (1H, d, J=8.0Hz), 8.31 (1H, s), 8.47 (1H, d, J=8.0Hz)

(3) To a suspension of 3-methyl-4-methylamino-8-

nitroquinoline (1.0 g) and triethylamine (2.8 g) in ethylene chloride (3 ml) was added triphosgene (1.37 g), and the mixture was stirred for 1.5 hours at 60°C. After cooled to ambient temperature, to the mixture was added 2M solution of dimethylamine in tetrahydrofuran (0.35 ml), and the mixture was stirred for 2 hours at ambient temperature. To the reaction mixture was added water, and the mixture was extracted with chloroform. The extract was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (ethyl acetate-n-hexane) to give 3-methyl-8-nitro-4-(1,3,3-trimethylureido)quinoline (545 mg) as an orange crystal.

mp : 163-165°C

NMR (DMSO-d_6, δ) : 2.32 (3H, s), 2.46 (2x3H, s), 3.10 (3H, s), 7.81 (1H, dd, J=8, 8Hz), 8.20 (1H, d, J=8Hz), 8.23 (1H, d, J=8Hz), 8.95 (1H, s)

(4) 8-Amino-3-methyl-4-(1,3,3-trimethylureido)quinoline was obtained according to a similar manner to that of Example 8-(2).

mp : 183-184°C

NMR (DMSO-d_6, δ) : 2.22 (3H, s), 2.44 (2x3H, s), 3.02 (3H, s), 5.98 (2H, s), 6.81 (1H, d, J=8Hz), 7.00 (1H, d, J=8Hz), 7.32 (1H, dd, J=8, 8Hz), 8.61 (1H, s)

(5) To a solution of 8-amino-3-methyl-4-(1,3,3-trimethylureido)quinoline (100 mg) in ethylene chloride (2 ml) were added triethylamine (97.9 mg) and 2,6-dichlorobenzoyl chloride (89.2 mg), and the mixture was stirred at 80°C overnight. The reaction mixture was diluted with chloroform, washed with saturated ammonium chloride solution, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated in vacuo. The

residue was purified by preparative thin layer chromatography (ethyl acetate). The residue was treated with hot ethanol, and the mixture was cooled to ambient temperature. The precipitate was collected by filtration to give 8-(2,6-dichlorobenzoylamino)-3-methyl-4-(1,3,3-trimethylureido)-quinoline (147 mg) as a white crystal.

mp : 163-165°C

NMR (DMSO-d_6, δ) : 2.30 (3H, s), 2.47 (2x3H, s), 3.08 (3H, s), 7.47-7.62 (3H, m), 7.66-7.75 (2H, m), 8.68 (1H, m), 8.80 (1H, s), 10.81 (1H, s)

Example 10

A mixture of 8-amino-3-methyl-4-(3-phenylureido)-quinoline (90 mg), 2,4-dimethylpyridine-3-carboxylic acid (69.8 mg), triethylamine (93.5 mg) and diphenyl chlorophosphate (207 mg) in ethylene chloride (1 ml) was refluxed for 5 hours. The reaction mixture was diluted with chloroform, washed with water and brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (methanol-chloroform). The residue was treated with hot ethanol, and the mixture was cooled to ambient temperature. The precipitate was collected by filtration to give 8-[(2,4-dimethylpyridin-3-yl)carbonylamino]-3-methyl-4-(3-phenylureido)quinoline (50 mg) as white powder.

mp : 233-235°C

NMR (DMSO-d_6, δ) : 2.36 (3H, s), 2.42 (3H, s), 2.50 (3H, s), 6.99 (1H, dd, J=8.0, 8.0Hz), 7.20 (1H, d, J=5.0Hz), 7.29 (2H, dd, J=8.0, 8.0Hz), 7.49 (2H, d, J=8.0Hz), 7.65 (1H, dd, J=8.0, 8.0Hz), 7.85 (1H, d, J=8.0Hz), 8.41 (1H, d, J=5.0Hz), 8.60 (1H, d, J=8.0Hz), 8.76 (1H, s), 8.90 (1H, br), 9.03 (1H, br), 10.45 (1H,s)

Example 11

The following compounds were obtained according to a similar manner to that of Example 10.

(1) 3-Methyl-4-(3-phenylureido)-8-[(4-trifluoromethyl-pyridin-3-yl)carbonylamino]quinoline
(from 8-amino-3-methyl-4-(3-phenylureido)quinoline and 4-trifluoromethylpyridine-3-carboxylic acid)
mp : 290-292°C
NMR (DMSO-d_6, δ) : 2.40 (3H, s), 6.98 (1H, dd, J=8.0, 8.0Hz), 7.28 (2H, dd, J=8.0, 8.0Hz), 7.50 (2H, d, J=8.0Hz), 7.65 (1H, d, J=8.0Hz), 7.85 (1H, d, J=8.0Hz), 7.91 (1H, d, J=6.0Hz), 8.62 (1H, d, J=8.0Hz), 8.78 (1H, s), 8.92 (1H, br), 9.00 (1H, d, J=6.0Hz), 9.06 (2H, br), 10.89 (1H, s)

(2) 8-[(3,5-Dichloropyridin-4-yl)carbonylamino]-3-methyl-4-(3-methylureido)quinoline
(from 8-amino-3-methyl-4-(3-methylureido)quinoline and 3,5-dichloropyridine-4-carboxylic acid)
mp : 243-245°C
NMR (DMSO-d_6, δ) : 2.33 (3H, s), 2.68 (3H, d, J=4.5Hz), 6.32 (1H, q, J=4.5Hz), 7.61 (1H, t, J=7.5Hz), 7.73 (1H, d, J=6.0Hz), 7.77 (1H, d, J=7.5Hz), 8.47 (1H, d, J=6.0Hz), 8.64 (1H, s), 8.65 (1H, d, J=7.5Hz), 8.73 (1H, s)

(3) 8-[(2,4-Dichloro-6-methylpyridin-3-yl)carbonylamino]-3-methyl-4-(3-propylureido)quinoline
(from 8-amino-3-methyl-4-(3-propylureido)quinoline and 2,4-dichloro-6-methylpyridine-3-carboxylic acid)
mp : 210-213°C
NMR (DMSO-d_6, δ) : 0.90 (3H, t, J=7Hz), 1.48 (2H, tq, J=7, 7Hz), 2.34 (3H, s), 2.53 (3H, s), 3.07 (2H, dt, J=7,6Hz), 6.43 (1H, t, J=6Hz), 7.56-7.65 (2H, m), 7.75 (1H, d, J=8Hz), 8.56 (1H, s), 8.64 (1H, d,

J=8Hz), 8.73 (1H, s), 11.03 (1H, s)

(4) 8-[(2,4-Dichloro-6-methylpyridin-3-yl)carbonylamino]-4-(3-isopropylureido)-3-methylquinoline
(from 8-amino-4-(3-isopropylureido)-3-methylquinoline and 2,4-dichloro-6-methylpyridine-3-carboxylic acid)
mp : 220-222°C
NMR (DMSO-d_6, δ) : 1.14 (6H, d, J=6.5Hz), 2.33 (3H, s), 2.54 (3H, s), 3.78 (1H, qqd, J=7.0, 6.5, 6.5Hz), 6.32 (1H, d, J=7.0Hz), 7.59-7.63 (2H, m), 7.75 (1H, d, J=8.0Hz), 8.48 (1H, s), 8.63 (1H, d, J=8.0Hz), 8.71 (1H, s), 11.02 (1H, s)

(5) 4-(3-Cyclopropylmethylureido)-8-[(2,4-dichloropyridin-3-yl)carbonylamino]-3-methylquinoline
(from 8-amino-4-(3-cyclopropylmethylureido)-3-methylquinoline and 2,4-dichloropyridine-3-carboxylic acid)
mp : 232-235°C
NMR (DMSO-d_6, δ) : 0.20-0.25 (2H, m), 0.43-0.50 (2H, m), 0.93-1.05 (1H, m), 2.35 (3H, s), 3.00 (2H, dd, J=7.5, 7.5Hz), 6.50 (1H, t, J=7.5Hz), 7.60 (1H, dd, J=8.0, 8.0Hz), 7.73 (1H, d, J=6.0Hz), 7.74 (1H, d, J=8.0Hz), 8.48 (1H, d, J=6.0Hz), 8.60 (1H, s), 8.67 (1H, d, J=8.0Hz), 8.75 (1H, s), 11.18 (1H, s)

(6) 8-[(2,4-Dichloropyridin-3-yl)carbonylamino]-4-[3-(2-methoxyethyl)ureido]-3-methylquinoline
(from 8-amino-4-[3-(2-methoxyethyl)ureido]-3-methylquinoline and 2,4-dichloropyridine-3-carboxylic acid)
mp : >300°C
NMR (DMSO-d_6, δ) : 2.36 (3H, s), 3.26-3.30 (2H, m), 3.33 (3H, s), 3.43 (2H, t, J=7.0Hz), 6.53 (1H, t, J=7.0Hz), 7.61 (1H, dd, J=8.0, 8.0Hz), 7.72 (1H, d, J=6.0Hz), 7.75 (1H, d, J=8.0Hz), 8.47 (1H, d, J=6.0Hz), 8.65 (1H, d, J=8.0Hz), 8.67 (1H, br),

8.73 (1H, s), 11.18 (1H, s)

(7) 8-[(2,4-Dimethylpyridin-3-yl)carbonylamino]-4-[3-(2-methoxyethyl)ureido]-3-methylquinoline
(from 8-amino-4-[3-(2-methoxyethyl)ureido]-3-methylquinoline and 2,4-dimethylpyridine-3-carboxylic acid)
mp : 211-215°C
NMR (DMSO-d_6, δ) : 2.34 (6H, s), 2.51 (3H, s), 3.25-3.30 (2H, m), 3.33 (3H, s), 3.43 (2H, t, J=5.0Hz), 6.53 (1H, t, J=5.0Hz), 7.20 (1H, d, J=6.0Hz), 7.61 (1H, dd, J=8.0, 8.0Hz), 7.74 (1H, d, J=8.0Hz), 8.40 (1H, d, J=6.0Hz), 8.57 (1H, d, J=8.0Hz), 8.67 (1H, s), 8.70 (1H, s)

(8) 8-[(2,4-Dichloro-6-methylpyridin-3-yl)carbonylamino]-4-[3-(2-methoxyethyl)ureido]-3-methylquinoline
(from 8-amino-4-[3-(2-methoxyethyl)ureido]-3-methylquinoline and 2,4-dichloro-6-methylpyridine-3-carboxylic acid)
mp : 226-228°C
NMR (DMSO-d_6, δ) : 2.35 (3H, s), 3.26-3.32 (2H, m), 3.35 (3H, s), 3.43 (2H, t, J=7.0Hz), 6.52 (1H, t, J=7.0Hz), 7.57-7.63 (2H, m), 7.73 (1H, d, J=8.0Hz), 8.63 (1H, d, J=8.0Hz), 8.65 (1H, s), 8.73 (1H, s), 11.03 (1H, s)

(9) 8-[(2,4-Dichloro-6-methylpyridin-3-yl)carbonylamino]-3-methyl-4-(3-phenylureido)quinoline
(from 8-amino-3-methyl-4-(3-phenylureido)quinoline and 2,4-dichloro-6-methylpyridine-3-carboxylic acid)
mp : 260-263°C
NMR (DMSO-d_6, δ) : 2.42 (3H, s), 2.53 (3H, s), 6.99 (1H, dd, J=8.0, 8.0Hz), 7.30 (2H, dd, J=8.0, 8.0Hz), 7.50 (2H, d, J=8.0Hz), 7.61-7.67 (2H, m), 7.84 (1H, d, J=8.0Hz), 8.67 (1H, d, J=8.0Hz), 8.78

(1H, s), 8.86 (1H, br), 9.00 (1H, br), 11.07 (1H, s)

(10) 3-Methyl-4-(3-phenylureido)-8-(2-trifluoromethylbenzoylamino)quinoline (from 8-amino-3-methyl-4-(3-phenylureido)quinoline and 2-(trifluoromethyl)benzoic acid)
mp : 270-273°C
NMR (DMSO-d_6, δ) : 2.40 (3H, s), 7.00 (1H, dd, J=8.0, 8.0Hz), 7.28 (2H, dd, J=8.0, 8.0Hz), 7.50 (2H, d, J=8.0Hz), 7.65 (1H, dd, J=8.0, 8.0Hz), 7.75-7.92 (5H, m), 8.62 (1H, d, J=8.0Hz), 8.75 (1H, s), 8.88 (1H, s), 9.03 (1H, s), 10.42 (1H, s)

(11) 8-[(2,4-Dimethylpyridin-3-yl)carbonylamino]-4-(1,3-dimethylureido)-3-methylquinoline (from 8-amino-4-(1,3-dimethylureido)-3-methylquinoline and 2,4-dimethylpyridine-3-carboxylic acid)
mp : 124-126°C
NMR (DMSO-d_6, δ) : 2.31 (3H, s), 2.34 (3H, s), 2.50 (3H, s), 2.50 (3H, d, J=4.5Hz), 3.12 (3H, s), 7.20 (1H, d, J=5.5Hz), 7.50 (1H, d, J=8.0Hz), 7.66 (1H, dd, J=8.0, 8.0Hz), 8.40 (1H, d, J=5.5Hz), 8.60 (1H, d, J=8.0Hz), 8.83 (1H, s), 10.48 (1H, s)

(12) 4-(1,3-Dimethylureido)-3-methyl-8-[(4-trifluoromethylpyridin-3-yl)carbonylamino]quinoline (from 8-amino-4-(1,3-dimethylureido)-3-methylquinoline and 4-(trifluoromethyl)pyridine-3-carboxylic acid)
mp : 110-113°C
NMR (DMSO-d_6, δ) : 2.32 (3H, s), 2.50 (3H, d, J=5.5Hz), 3.13 (3H, s), 7.52 (1H, d, J=8.0Hz), 7.68 (1H, dd, J=8.0, 8.0Hz), 7.90 (1H, d, J=5.5Hz), 8.63 (1H, d, J=8.0Hz), 8.85 (1H, s), 8.99 (1H, d, J=5.5Hz), 9.03 (1H, s), 10.93 (1H, s)

(13) 3-Methyl-8-[(4-trifluoromethylpyridin-3-yl)-carbonylamino]-4-(1,3,3-trimethylureido)quinoline (from 8-amino-3-methyl-4-(1,3,3-trimethylureido)-quinoline and 4-(trifluoromethyl)pyridine-3-carboxylic acid)

mp : 85-87°C

NMR (DMSO-d_6, δ) : 2.29 (3H, s), 2.45 (2x3H, s), 3.07 (3H, s), 7.65-7.75 (2H, m), 7.88 (1H, d, J=5Hz), 8.63 (1H, m), 8.80 (1H, s), 8.98 (1H, d, J=5Hz), 9.03 (1H, s), 10.90 (1H, s)

(14) 8-[(2,4-Dimethylpyridin-3-yl)carbonylamino]-3-methyl-4-(1-methyl-3-phenylureido)quinoline (from 8-amino-3-methyl-4-(1-methyl-3-phenylureido)-quinoline and 2,4-dimethylpyridine-3-carboxylic acid)

mp : 117-119°C

NMR ($CDCl_3$, δ) : 2.45 (3H, s), 2.50 (3H, s), 2.68 (3H, s), 3.37 (3H, s), 5.80 (1H, br s), 6.97-7.05 (1H, m), 7.10 (1H, d, J=5.5Hz), 7.16-7.24 (4H, m), 7.65 (1H, d, J=7.5Hz), 7.71 (1H, t, J=7.5Hz), 8.47 (1H, d, J=5.5Hz), 8.77 (1H, s), 8.99 (1H, d, J=7.5Hz), 9.93 (1H, s)

Example 12

(1) 3-Chloro-8-nitro-4-(3-phenylureido)quinoline was obtained from 4-amino-3-chloro-8-nitroquinoline and aniline according to a similar manner to that of Example 9-(3).

NMR (DMSO-d_6, δ) : 7.02 (1H, t, J=8Hz), 7.30 (2H, t, J=8Hz), 7.60 (2H, d, J=8Hz), 7.81 (1H, t, J=8Hz), 8.31 (2H, d, J=8Hz), 9.18-9.27 (1H, br), 9.28 (1H, s)

(2) 8-Amino-3-chloro-4-(3-phenylureido)quinoline was obtained according to a similar manner to that of Example 5-(4).

NMR ($DMSO-d_6$, δ) : 6.04 (2H, s), 6.88 (1H, d, J=8Hz), 6.98 (1H, t, J=8Hz), 7.14 (1H, d, J=8Hz), 7.23-7.39 (3H, m), 7.48 (2H, d, J=8Hz), 8.71 (1H, s), 8.80 (1H, s), 9.06 (1H, s)

(3) 3-Chloro-8-[(2,4-dichloropyridin-3-yl)carbonylamino]-4-(3-phenylureido)quinoline was obtained from 8-amino-3-chloro-4-(3-phenylureido)quinoline and 2,4-dichloropyridine-3-carboxylic acid according to a similar manner to that of Example 10.

mp : 213-215°C

NMR ($DMSO-d_6$, δ) : 7.01 (1H, t, J=8Hz), 7.26-7.35 (2H, m), 7.47-7.53 (2H, m), 7.70-7.78 (2H, m), 7.88 (1H, d, J=8Hz), 8.48 (1H, d, J=5Hz), 8.76 (1H, d, J=8Hz), 8.92 (1H, s), 9.10 (1H, s), 9.18 (1H, s)

Example 13

A mixture of 8-(2,6-dichlorobenzoylamino)-3-methyl-4-[3-(4-nitrophenyl)ureido]quinoline (100 mg) and platinum oxide (15 mg) in ethanol (10 ml) was stirred under hydrogen atmosphere at ambient temperature for 1.5 hours. Insoluble material was filtered off, and the filtrate was concentrated in vacuo. The residue was treated with hot ethanol, and the mixture was cooled to ambient temperature. The precipitate was collected by filtration to give 4-[3-(4-aminophenyl)-ureido]-8-(2,6-dichlorobenzoylamino)-3-methylquinoline (57 mg).

mp : 244-248°C

NMR ($DMSO-d_6$, δ) : 2.42 (3H, s), 7.49-7.78 (8H, m), 7.85 (1H, d, J=8Hz), 8.21 (2H, d, J=8Hz), 8.68 (1H, d, J=8Hz), 8.82 (1H, s), 9.10-9.18 (1H, br), 9.73-9.80 (1H, br)

Example 14

(1) 3-Methyl-8-nitro-4-ureidoquinoline was obtained from

4-amino-3-methyl-8-nitroquinoline and 7N solution of ammonia in methanol according to a similar manner to that of Example 5-(3).

mp : 212.5-214°C

NMR (DMSO-d_6, δ) : 2.38 (3H, s), 6.23 (2H, s), 7.71 (1H, t, J=7.5Hz), 8.15 (1H, d, J=7.5Hz), 8.21 (1H, d, J=7.5Hz), 8.78 (1H, br s), 8.86 (1H, s)

(2) 8-Amino-3-methyl-4-ureidoquinoline was obtained from 3-methyl-8-nitro-4-ureidoquinoline according to a similar manner to that of Example 5-(4).

mp : 223-225°C

NMR (DMSO-d_6, δ) : 2.29 (3H, s), 5.85 (2H, s), 6.01 (2H, s), 6.78 (1H, d, J=7.5Hz), 7.10 (1H, d, J=7.5Hz), 7.25 (1H, t, J=7.5Hz), 8.40 (1H, s), 8.53 (1H, s)

(3) 8-[(2,4-Dichloropyridin-3-yl)carbonylamino]-3-methyl-4-ureidoquinoline was obtained from 8-amino-3-methyl-4-ureidoquinoline and 2,4-dichloropyridine-3-carboxylic acid according to a similar manner to that of Example 10.

mp : 202-202.5°C

NMR (DMSO-d_6, δ) : 2.35 (3H, s), 6.12 (2H, s), 7.62 (1H, t, J=7.5Hz), 7.73 (1H, d, J=6.0Hz), 7.78 (1H, d, J=7.5Hz), 8.47 (1H, d, J=6.0Hz), 8.65 (1H, s), 8.66 (1H, d, J=7.5Hz), 8.74 (1H, s)

<u>Example 15</u>

(1) 4-(3-Ethylureido)-3-methyl-8-nitroquinoline was obtained from 4-amino-3-methyl-8-nitroquinoline and 2M solution of ethylamine in tetrahydrofuran according to a similar manner to that of Example 5-(3).

NMR (DMSO-d_6, δ) : 1.09 (3H, t, J=8Hz), 2.38 (3H, s), 3.13 (2H, dq, J=5, 8Hz), 6.52 (1H, t, J=5Hz), 7.70 (1H, t, J=8Hz), 8.17 (1H, d, J=8Hz), 8.19 (1H, d,

J=8Hz), 8.70 (1H, s), 8.87 (1H, s)

(2) 8-Amino-4-(3-ethylureido)-3-methylquinoline was obtained from 4-(3-ethylureido)-3-methyl-8-nitroquinoline according to a similar manner to that of Example 5-(4).

NMR (DMSO-d_6, δ) : 1.07 (3H, t, J=8Hz), 2.29 (3H, s), 3.12 (2H, dq, J=5, 8Hz), 5.88 (2H, s), 6.30 (1H, t, J=5Hz), 6.78 (1H, d, J=8Hz), 7.09 (1H, d, J=8Hz), 7.25 (1H, t, J=8Hz), 8.30 (1H, s), 8.53 (1H, s)

(3) To a solution of 4-(trifluoromethyl)pyridine-3-carboxylic acid (93.9 mg) and triethylamine (62.1 mg) in dichloroethane (15 ml) was added diphenyl chlorophosphate (165 mg) at ambient temperature and the mixture was stirred for 30 minutes. To the mixture were added 8-amino-4-(3-ethylureido)-3-methylquinoline (100 mg) and 4-dimethylaminopyridine (10 mg), and the mixture was stirred at ambient temperature for 20 hours. The resulting mixture was diluted with chloroform and methanol, and the organic layer was washed with water, dried over magnesium sulfate and concentrated in vacuo. The residual solid was treated with hot acetonitrile, collected by filtration and washed with acetonitrile to give 4-(3-ethylureido)-3-methyl-8-[(4-trifluoromethylpyridin-3-yl)carbonylamino]quinoline (107 mg).

mp : 256-262°C

NMR (DMSO-d_6, δ) : 1.09 (3H, t, J=8Hz), 2.33 (3H, s), 3.14 (2H, dq, J=5, 8Hz), 6.41 (1H, t, J=5Hz), 7.61 (1H, t, J=8Hz), 7.77 (1H, d, J=8Hz), 7.89 (1H, d, J=5Hz), 8.58 (1H, s), 8.59 (1H, d, J=8Hz), 8.72 (1H, s), 8.98 (1H, d, J=5Hz), 9.06 (1H, s)

Example 16

The following compounds were obtained according to a similar manner to that of Example 15-(3).

(1) 8-[(2,4-Dichloropyridin-3-yl)carbonylamino]-4-(3-ethylureido)-3-methylquinoline
(from 8-amino-4-(3-ethylureido)-3-methylquinoline and 2,4-dichloropyridine-3-carboxylic acid)
mp : 241-244°C
NMR (DMSO-d_6, δ) : 1.09 (3H, t, J=8Hz), 2.35 (3H, s), 3.15 (2H, dq, J=5, 8Hz), 6.41 (1H, t, J=5Hz), 7.62 (1H, t, J=8Hz), 7.72 (1H, d, J=5Hz), 7.77 (1H, d, J=8Hz), 8.48 (1H, d, J=5Hz), 8.58 (1H, s), 8.67 (1H, d, J=8Hz), 8.73 (1H, s)

(2) 8-[(2,4-Dichloro-6-methylpyridin-3-yl)carbonylamino]-4-(3-ethylureido)-3-methylquinoline
(from 8-amino-4-(3-ethylureido)-3-methylquinoline and 2,4-dichloro-6-methylpyridine-3-carboxylic acid)
mp : 242-245°C
NMR (DMSO-d_6, δ) : 1.49 (3H, t, J=8Hz), 2.36 (3H, s), 2.53 (3H, s), 3.15 (2H, dq, J=4, 8Hz), 6.40 (1H, t, J=4Hz), 7.60 (1H, t, J=8Hz), 7.62 (1H, s), 7.77 (1H, d, J=8Hz), 8.58 (1H, s), 8.66 (1H, d, J=8Hz), 8.73 (1H, s)

Example 17

(1) 3-Methyl-8-nitro-4-(3-propylureido)quinoline was obtained from 4-amino-3-methyl-8-nitroquinoline and n-propylamine according to a similar manner to that of Example 3-(4).
mp : 186-190°C
NMR (DMSO-d_6, δ) : 0.90 (3H, t, J=7Hz), 1.48 (2H, tq, J=7, 7Hz), 2.36 (3H, s), 3.08 (2H, dt, J=7, 6Hz), 6.55 (1H, t, J=6Hz), 7.71 (1H, dd, J=8, 8Hz), 8.15 (1H, d, J=8Hz), 8.19 (1H, d, J=8Hz), 8.69 (1H, s), 8.85 (1H, s)

(2) 8-Amino-3-methyl-4-(3-propylureido)quinoline was

obtained from 3-methyl-8-nitro-4-(3-propylureido)quinoline according to a similar manner to that of Example 5-(4).

mp : 260°C

NMR (DMSO-d_6, δ) : 0.89 (3H, t, J=7Hz), 1.46 (2H, tq, J=7, 7Hz), 2.28 (3H, s), 3.05 (2H, dt, J=7, 6Hz), 5.86 (2H, s), 6.34 (1H, t, J=6Hz), 6.77 (1H, d, J=8Hz), 7.57 (1H, d, J=8Hz), 7.65 (1H, dd, J=8, 8Hz), 8.29 (1H, s), 8.55 (1H, s)

(3) 8-[(2,4-Dichloropyridin-3-yl)carbonylamino]-3-methyl-4-(3-propylureido)quinoline was obtained from 8-amino-3-methyl-4-(3-propylureido)quinoline and 2,4-dichloropyridine-3-carboxylic acid according to a similar manner to that of Example 10.

mp : 247-253°C

NMR (DMSO-d_6, δ) : 0.90 (3H, t, J=7Hz), 1.48 (2H, tq, J=7, 7Hz), 2.35 (3H, s), 3.08 (2H, dt, J=7, 6Hz), 6.43 (1H, t, J=6Hz), 7.61 (1H, dd, J=8, 8Hz), 7.72 (1H, d, J=6Hz), 7.77 (1H, d, J=8Hz), 8.47 (1H, d, J=6Hz), 8.55 (1H, s), 8.65 (1H, d, J=8Hz), 8.72 (1H, s), 11.18 (1H, s)

Example 18

(1) 4-(3-Isopropylureido)-3-methyl-8-nitroquinoline was obtained from 4-amino-3-methyl-8-nitroquinoline and isopropylamine according to a similar manner to that of Example 3-(4).

mp : 215-215.5°C

NMR (DMSO-d_6, δ) : 1.12 (6H, d, J=7.0Hz), 2.35 (3H, s), 3.78 (1H, m), 6.42 (1H, d, J=7.5Hz), 7.70 (1H, t, J=7.5Hz), 8.15 (1H, d, J=7.5Hz), 8.18 (1H, d, J=7.5Hz), 8.59 (1H, s), 8.85 (1H, s)

(2) 8-Amino-4-(3-isopropylureido)-3-methylquinoline was obtained from 4-(3-isopropylureido)-3-methyl-8-nitroquinoline

according to a similar manner to that of Example 5-(4).

mp : 237-240°C

NMR (DMSO-d_6, δ) : 2.28 (3H, s), 2.66 (3H, d, J=4.5Hz), 5.84 (2H, s), 6.20 (1H, q, J=4.5Hz), 6.77 (1H, d, J=7.5Hz), 7.07 (1H, d, J=7.5Hz), 7.23 (1H, t, J=7.5Hz), 8.34 (1H, s), 8.54 (1H, s)

(3) 8-[(2,4-Dichloropyridin-3-yl)carbonylamino]-4-(3-isopropylureido)-3-methylquinoline was obtained from 8-amino-4-(3-isopropylureido)-3-methylquinoline and 2,4-dichloropyridine-3-carboxylic acid according to a similar manner to that of Example 10.

mp : 235-236°C

NMR (DMSO-d_6, δ) : 1.16 (6H, d, J=7.0Hz), 2.33 (3H, s), 3.78 (1H, m), 6.33 (1H, d, J=7.5Hz), 7.62 (1H, t, J=7.5Hz), 7.69-7.81 (2H, m), 8.44-8.55 (2H, m), 8.66 (1H, d, J=7.5Hz), 8.73 (1H, s)

Example 19

(1) 8-Amino-3-methyl-4-(4-toluenesulfonamido)quinoline was obtained from 3-methyl-8-nitro-4-(4-toluenesulfonamido)-quinoline according to a similar manner to that of Example 8-(2).

NMR (DMSO-d_6, δ) : 2.13 (3H, s), 2.37 (3H, s), 5.86 (2H, br s), 6.71 (1H, d, J=9Hz), 6.84 (1H, br d, J=9Hz), 7.04 (1H, t, J=9Hz), 7.33 (2H, d, J=8Hz), 7.51 (2H, d, J=8Hz), 8.56 (1H, s), 9.96 (1H, br s)

(2) 8-[(2,4-Dichloropyridin-3-yl)carbonylamino]-3-methyl-4-(4-toluenesulfonamido)quinoline was obtained from 8-amino-3-methyl-4-(4-toluenesulfonamido)quinoline and 2,4-dichloropyridine-3-carboxylic acid according to a similar manner to that of Example 5-(5).

mp : 275°C

NMR (DMSO-d_6, δ) : 2.14 (3H, s), 2.38 (3H, s), 7.35

(2H, d, J=7Hz), 7.41 (1H, t, J=9Hz), 7.47-7.59 (3H, m), 7.70 (1H, d, J=5Hz), 8.47 (1H, d, J=5Hz), 8.59 (1H, d, J=9Hz), 8.76 (1H, s)

(3) 4-Amino-8-[(2,4-dichloropyridin-3-yl)carbonylamino]-3-methylquinoline was obtained from 8-[(2,4-dichloropyridin-3-yl)carbonylamino]-3-methyl-4-(4-toluenesulfonamido)quinoline according to a similar manner to that of Example 5-(2).

mp : 126-129°C

NMR (DMSO-d_6, δ) : 2.21 (3H, s), 7.42-7.53 (1H, m), 7.75 (1H, d, J=5.5Hz), 8.02-8.13 (1H, m), 8.30 (1H, s), 8.47-8.57 (1H, m), 8.49 (1H, d, J=5.5Hz)

(4) 4-(3-Butylureido)-8-[(2,4-dichloropyridin-3-yl)-carbonylamino]-3-methylquinoline was obtained from 4-amino-8-[(2,4-dichloropyridin-3-yl)carbonylamino]-3-methylquinoline and butylamine according to a similar manner to that of Example 3-(4).

mp : 241-246°C

NMR (DMSO-d_6, δ) : 0.90 (3H, t, J=8Hz), 1.26-1.53 (4H, m), 2.34 (3H, s), 3.10 (2H, q, J=8Hz), 6.41 (1H, t, J=7Hz), 7.60 (1H, t, J=9Hz), 7.69-7.80 (2H, m), 8.47 (1H, d, J=5Hz), 8.56 (1H, s), 8.66 (1H, d, J=9Hz), 8.73 (1H, s)

Example 20

(1) 4-[3-(2-Methoxyethyl)ureido]-3-methyl-8-nitroquinoline was obtained from 4-amino-3-methyl-8-nitroquinoline and 2-methoxyethylamine according to a similar manner to that of Example 3-(4).

mp : 270-271°C

NMR (DMSO-d_6, δ) : 2.36 (3H, s), 3.26-3.30 (2H, dt, J=6.5, 6.0Hz), 3.40-3.44 (2H, t, J=6.5Hz), 6.65 (1H, t, J=6.0Hz), 7.70 (1H, dd, J=8.0, 8.0Hz), 8.15 (1H, d, J=8.0Hz), 8.80 (1H, s), 8.86 (1H, s)

(2) 8-Amino-4-[3-(2-methoxyethyl)ureido]-3-methylquinoline was obtained from 4-[3-(2-methoxyethyl)ureido]-3-methyl-8-nitroquinoline according to a similar manner to that of Example 5-(4).

mp : 266-269°C

NMR (DMSO-d_6, δ) : 2.28 (3H, s), 3.23-3.32 (2H, m), 3.33 (3H, s), 3.42 (2H, t, J=6.0Hz), 5.87 (2H, s), 6.46 (1H, t, J=7.0Hz), 6.78 (1H, d, J=8.0Hz), 7.07 (1H, d, J=8.0Hz), 7.26 (1H, dd, J=8.0, 8.0Hz), 8.40 (1H, s), 8.54 (1H, s)

(3) 4-[3-(2-Methoxyethyl)ureido]-3-methyl-8-[(4-trifluoromethylpyridin-3-yl)carbonylamino]quinoline was obtained from 8-amino-4-[3-(2-methoxyethyl)ureido]-3-methylquinoline and 4-(trifluoromethyl)pyridine-3-carboxylic acid according to a similar manner to that of Example 10.

mp : >300°C

NMR (DMSO-d_6, δ) : 2.36 (3H, s), 3.27-3.30 (2H, m), 3.34 (3H, s), 3.43 (2H, t, J=6.0Hz), 6.53 (1H, t, J=6.0Hz), 7.61 (1H, dd, J=8.0, 8.0Hz), 7.75 (1H, d, J=8.0Hz), 7.90 (1H, d, J=6.0Hz), 8.60 (1H, d, J=8.0Hz), 8.68 (1H, s), 8.74 (1H, s), 9.00 (1H, d, J=6.0Hz), 9.05 (1H, s)

Example 21

(1) 3-Chloro-8-nitro-4-(4-toluenesulfonamido)quinoline was obtained from 3-chloro-1,4-dihydro-8-nitro-4-oxoquinoline and p-toluenesulfonyl isocyanate according to a similar manner to that of Example 5-(1).

mp : 204.5-206°C

NMR (DMSO-d_6, δ) : 2.40 (3H, s), 7.37 (2H, d, J=7.5Hz), 7.58 (2H, d, J=7.5Hz), 7.78 (1H, t, J=7.5Hz), 8.23 (1H, d, J=7.5Hz), 8.32 (1H, d, J=7.5Hz), 9.03 (1H, s)

(2) 4-Amino-3-chloro-8-nitroquinoline was obtained from 3-chloro-8-nitro-4-(4-toluenesulfonamido)quinoline according to a similar manner to that of Example 5-(2).

mp : 220-222°C

NMR (DMSO-d_6, δ) : 7.47 (2H, br s), 7.58 (1H, t, J=7.5Hz), 8.11 (1H, d, J=7.5Hz), 8.51 (1H, s), 8.56 (1H, d, J=7.5Hz)

(3) 3-Chloro-4-(3-methylureido)-8-nitroquinoline was obtained from 4-amino-3-chloro-8-nitroquinoline and 2M solution of methylamine in tetrahydrofuran according to a similar manner to that of Example 3-(4).

mp : 213.5-214°C

NMR (DMSO-d_6, δ) : 2.69 (3H, d, J=5.5Hz), 6.69 (1H, q, J=5.5Hz), 7.77 (1H, t, J=7.5Hz), 8.18 (1H, d, J=7.5Hz), 8.27 (1H, d, J=7.5Hz), 9.01 (2H, s)

(4) 8-Amino-3-chloro-4-(3-methylureido)quinoline was obtained from 3-chloro-4-(3-methylureido)-8-nitroquinoline according to a similar manner to that of Example 8-(2).

mp : 232-233°C

NMR (DMSO-d_6, δ) : 2.67 (3H, d, J=4.5Hz), 5.98 (2H, s), 6.38 (1H, q, J=4.5Hz), 6.84 (1H, d, J=7.5Hz), 7.05 (1H, d, J=7.5Hz), 7.31 (1H, t, J=7.5Hz), 8.58 (1H, s), 8.65 (1H, s)

(5) 3-Chloro-8-[(2,4-dichloropyridin-3-yl)carbonylamino]-4-(3-methylureido)quinoline was obtained from 8-amino-3-chloro-4-(3-methylureido)quinoline and 2,4-dichloropyridine-3-carboxylic acid according to a similar manner to that of Example 10.

mp : 238-239°C

NMR (DMSO-d_6, δ) : 2.69 (3H, d, J=5.5Hz), 6.53 (1H, q, J=5.5Hz), 7.67 (1H, t, J=7.5Hz), 7.73 (1H, d, J=5.5Hz), 7.76 (1H, d, J=7.5Hz), 8.48 (1H, d,

J=5.5Hz), 8.71 (1H, d, J=7.5Hz), 8.86 (1H, s), 8.87 (1H, s)

Example 22

8-[(2-Chloropyridin-3-yl)carbonylamino]-4-(3,3-dimethylureido)-3-methylquinoline was obtained from 8-amino-4-(3,3-dimethylureido)-3-methylquinoline and 2-chloropyridine-3-carboxylic acid according to a similar manner to that of Example 7-(3).

mp : 135-140°C

NMR (DMSO-d_6, δ) : 2.32 (3H, s), 3.02 (6H, s), 7.57-7.67 (2H, m), 7.77 (1H, d, J=8Hz), 8.20 (1H, d, J=8Hz), 8.53-8.61 (2H, m), 8.65 (1H, d, J=8Hz), 8.78 (1H, s)

Example 23

(1) 3-Methyl-8-nitro-4-(piperidinocarbonylamino)quinoline was obtained from 4-amino-3-methyl-8-nitroquinoline and piperidine according to a similar manner to that of Example 5-(3).

NMR (DMSO-d_6, δ) : 1.51-1.71 (6H, m), 2.33 (3H, s), 3.46-3.57 (4H, m), 7.71 (1H, t, J=8Hz), 8.17 (1H, d, J=8Hz), 8.19 (1H, d, J=8Hz), 8.81 (1H, s), 8.88 (1H, s)

(2) 8-Amino-3-methyl-4-(piperidinocarbonylamino)quinoline was obtained from 3-methyl-8-nitro-4-(piperidinocarbonylamino)quinoline according to a similar manner to that of Example 5-(4).

NMR (DMSO-d_6, δ) : 1.48-1.70 (6H, m), 2.26 (3H, s), 3.44-3.58 (4H, m), 5.86 (2H, s), 6.78 (1H, d, J=8Hz), 7.06 (1H, d, J=8Hz), 7.24 (1H, t, J=8Hz), 8.44 (1H, s), 8.58 (1H, s)

(3) 3-Methyl-4-(piperidinocarbonylamino)-8-[(4-

trifluoromethylpyridin-3-yl)carbonylamino]quinoline was obtained from 8-amino-3-methyl-4-(piperidinocarbonylamino)-quinoline and 4-(trifluoromethyl)pyridine-3-carboxylic acid according to a similar manner to that of Example 15-(3).

mp : 185-188°C

NMR (DMSO-d_6, δ) : 1.51-1.70 (6H, m), 2.32 (3H, s), 3.48-3.58 (4H, m), 7.62 (1H, t, J=8Hz), 7.76 (1H, d, J=8Hz), 7.91 (1H, d, J=5Hz), 8.60 (1H, d, J=8Hz), 8.70 (1H, s), 8.76 (1H, s), 8.99 (1H, d, J=5Hz), 9.07 (1H, s)

Example 24

(1) 4-(1,3-Dimethylureido)-3-methyl-8-nitroquinoline was obtained from 3-methyl-4-methylamino-8-nitroquinoline and 2M solution of methylamine in tetrahydrofuran according to a similar manner to that of Example 3-(4).

mp : 199-201°C

NMR (DMSO-d_6, δ) : 2.34 (3H, s), 3.15 (3H, s), 7.76 (1H, dd, J=8.0, 8.0Hz), 7.97 (1H, d, J=8.0Hz), 8.21 (1H, d, J=8.0Hz), 9.00 (1H, s)

(2) 8-Amino-4-(1,3-dimethylureido)-3-methylquinoline was obtained from 4-(1,3-dimethylureido)-3-methyl-8-nitroquinoline according to a similar manner to that of Example 8-(2).

mp : 193-195°C

NMR (DMSO-d_6, δ) : 2.25 (3H, s), 3.06 (3H, s), 5.94 (2H, s), 6.78 (1H, d, J=8.0Hz), 6.80 (1H, d, J=8.0Hz), 7.27 (1H, dd, J=8.0, 8.0Hz), 8.64 (1H, s)

(3) 8-(2,6-Dichlorobenzoylamino)-4-(1,3-dimethylureido)-3-methylquinoline was obtained from 8-amino-4-(1,3-dimethyl-ureido)-3-methylquinoline and 2,6-dichlorobenzoyl chloride according to a similar manner to that of Example 9-(5).

mp : 92-102°C

NMR (DMSO-d_6, δ) : 2.30 (3H, s), 2.49 (3H, s), 3.12 (3H, s), 7.48-7.60 (5H, m), 7.64-7.70 (2H, m), 8.67 (1H, d, J=8.0Hz), 8.85 (1H, s), 10.79 (1H, s)

Example 25

(1) 3-Methyl-4-(1-methyl-3-phenylureido)-8-nitroquinoline was obtained from 3-methyl-4-methylamino-8-nitroquinoline and aniline according to a similar manner to that of Example 3-(4).

mp : 238.5-240°C

NMR (DMSO-d_6, δ) : 2.39 (3H, s), 3.24 (3H, br s), 6.94 (1H, m), 7.14-7.24 (2H, m), 7.27-7.40 (2H, m), 7.79 (1H, t, J=7.5Hz), 8.11 (1H, d, J=7.5Hz), 8.23 (1H, d, J=7.5Hz), 9.03 (1H, s)

(2) 8-Amino-3-methyl-4-(1-methyl-3-phenylureido)quinoline was obtained from 3-methyl-4-(1-methyl-3-phenylureido)-8-nitroquinoline according to a similar manner to that of Example 5-(4).

mp : 280-281°C

NMR (DMSO-d_6, δ) : 2.33 (3H, s), 3.16 (3H, br s), 5.99 (2H, br s), 6.81 (1H, d, J=7.5Hz), 6.86-6.97 (1H, m), 6.89 (1H, d, J=7.5Hz), 7.10-7.22 (2H, m), 7.26-7.39 (2H, m), 7.30 (1H, t, J=7.5Hz), 7.78 (1H, m), 8.70 (1H, s)

(3) 8-[(2,4-Dichloropyridin-3-yl)carbonylamino]-3-methyl-4-(1-methyl-3-phenylureido)quinoline was obtained from 8-amino-3-methyl-4-(1-methyl-3-phenylureido)quinoline and 2,4-dichloropyridine-3-carboxylic acid according to a similar manner to that of Example 5-(5).

mp : 122-124°C

NMR (DMSO-d_6, δ) : 2.38 (3H, s), 3.23 (3H, br s), 6.93 (1H, m), 7.13-7.24 (2H, m), 7.26-7.40 (2H, m), 7.63 (1H, t, J=7.5Hz), 7.71 (1H, d, J=7.5Hz), 7.73 (1H,

d, J=5.5Hz), 7.89 (1H, m), 8.48 (1H, d, J=5.5Hz), 8.73 (1H, d, J=7.5Hz), 8.91 (1H, s)

Example 26

The following compounds were obtained according to a similar manner to that of Example 9-(5).

(1) 4-[3-(2-Methoxyethyl)ureido]-3-methyl-8-(2-trifluoromethylbenzoylamino)quinoline
(from 8-amino-3-methyl-4-[3-(2-methoxyethyl)ureido]-quinoline and 2-(trifluoromethyl)benzoyl chloride)
mp : 254-259°C
NMR (DMSO-d_6, δ) : 2.34 (3H, s), 3.26-3.30 (2H, m), 3.35 (3H, s), 3.44 (2H, t, J=6.0Hz), 6.58 (1H, t, J=7.0Hz), 7.60 (1H, dd, J=8.0, 8.0Hz), 7.70-7.78 (2H, m), 7.84-7.86 (2H, m), 7.90 (1H, d, J=8.0Hz), 8.60 (1H, d, J=8.0Hz), 8.70 (1H, s), 8.73 (1H, s), 10.34 (1H, s)

(2) 8-(2,6-Dichlorobenzoylamino)-3-methyl-4-(1-methyl-3-phenylureido)quinoline
(from 8-amino-3-methyl-4-(1-methyl-3-phenylureido)-quinoline and 2,6-dichlorobenzoyl chloride)
mp : 91-95°C
NMR ($CDCl_3$, δ) : 2.36 (3H, s), 2.49 (3H, s), 5.78 (1H, br s), 6.97-7.04 (1H, m), 7.16-7.24 (4H, m), 7.32-7.45 (3H, m), 7.65 (1H, d, J=7.5Hz), 7.71 (1H, t, J=7.5Hz), 8.79 (1H, s), 9.00 (1H, d, J=7.5Hz), 10.01 (1H, s)

Example 27

To a solution of 8-amino-3-methyl-4-(3-methylureido)-quinoline (100 mg) in 1,2-dichloroethane (3 ml) was added 4-nitrophenyl isocyanate (78.4 mg) at ambient temperature under nitrogen atmosphere. The reaction mixture was stirred at

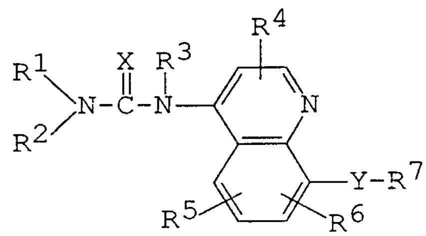
70°C for 3 hours. After cooled to ambient temperature, the precipitate was collected. The solid was washed with ethanol and aqueous N,N-dimethylformamide to give 3-methyl-4-(3-methylureido)-8-[3-(4-nitrophenyl)ureido]quinoline (77.4 mg) as a yellow solid.

mp : 250.5-252°C

NMR (DMSO-d_6, δ) : 2.36 (3H, s), 2.69 (3H, d, J=5.0Hz), 6.34 (1H, q, J=5.0Hz), 7.53 (1H, t, J=7.5Hz), 7.60 (1H, d, J=7.5Hz), 7.77 (2H, d, J=9.0Hz), 8.23 (2H, d, J=9.0Hz), 8.49 (1H, d, J=7.5Hz), 8.63 (1H, s), 8.77 (1H, s), 9.90 (1H, s), 10.59 (1H, s)

C L A I M S

1. A compound of the formula :



wherein

R^1 is hydrogen; lower alkyl which may be substituted with substituent(s) selected from the group consisting of hydroxy, lower alkoxy, acyl, cyclo(lower)alkyl, halogen, aryl and a heterocyclic group;
lower alkenyl; cyclo(lower)alkyl;
amino; lower alkylamino;
substituted or unsubstituted aryl; or
substituted or unsubstituted heterocyclic group;
and

R^2 is hydrogen; or lower alkyl which may be substituted with a substituent selected from the group consisting of hydroxy and lower alkoxy;
or

R^1 and R^2 are taken together with the attached nitrogen atom to form substituted or unsubstituted N-containing heterocyclic-N-yl group,

R^3 is hydrogen or lower alkyl,

R^4 is hydrogen, halogen, cyano or lower alkyl which may be substituted with a substituent selected from the group consisting of hydroxy and lower alkoxy,

R^5 and R^6 are each hydrogen, halogen, lower alkyl, lower alkoxy or halo(lower)alkyl,

R^7 is a heterocyclic group or aryl, each of which may be substituted with substituent(s) selected from the group consisting of halogen, nitro, lower alkyl, lower alkoxy, hydroxy, ar(lower)alkoxy and halo(lower)alkyl,

X is O or S,

and

Y is -NHCO-, -CONH- or $-NH\overset{\overset{X^1}{\|}}{C}NH-$,

in which X^1 is O or S,

and pharmaceutically acceptable salts thereof.

2. A compound of claim 1, wherein

R^1 is hydrogen; lower alkyl which may be substituted with substituent(s) selected from the group consisting of hydroxy, lower alkoxy, lower alkoxycarbonyl, cyclo(lower)alkyl, halogen, aryl and a heterocyclic group;

lower alkenyl; cyclo(lower)alkyl; amino; lower alkylamino; aryl may be substituted with substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halo(lower)alkyl, lower alkoxycarbonyl, nitro, amino and halogen; or a heterocyclic group may be substituted with substituent(s) selected from the group consisting of lower alkyl, halogen, oxo and lower alkoxycarbonyl;

and

R^2 is hydrogen; or lower alkyl which may be substituted with a substituent selected from the group consisting of hydroxy and lower alkoxy;

or

R^1 and R^2 are taken together with the attached nitrogen atom to form N-containing heterocyclic-N-yl group may be substituted with a substituent selected from the group consisting of lower alkyl and lower

alkanoyl.

3. A compound of claim 2, wherein
R^1 is hydrogen; lower alkyl; hydroxy(lower)alkyl; lower alkoxy(lower)alkyl; carboxy(lower)alkyl; lower alkoxycarbonyl(lower)alkyl; cyclo(lower)alkyl(lower)alkyl; halo(lower)alkyl; benzyl; phenethyl; pyridyl(lower)alkyl; piperidyl(lower)alkyl; lower alkenyl; cyclo(lower)alkyl; amino; lower alkylamino; phenyl or naphthyl, each of which may be substituted with substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halo(lower)alkyl, lower alkoxycarbonyl, nitro, amino and halogen; or pyridyl, pyrimidinyl, quinolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, morpholinyl, thienyl, tetrahydrofuryl or pyrrolidinyl, each of which may be substituted with substituent(s) selected from the group consisting of lower alkyl, halogen, oxo and lower alkoxycarbonyl;
and
R^2 is hydrogen; or lower alkyl which may be substituted with a substituent selected from the group consisting of hydroxy and lower alkoxy;
or
R^1 and R^2 are taken together with the attached nitrogen atom to form morpholino, thiomorpholino, piperidino, 1-piperazinyl or 1-pyrrolidinyl, each of which may be substituted with a substituent selected from the group consisting of lower alkyl and lower alkanoyl,
R^7 is pyridyl or phenyl, each of which may be substituted with substituent(s) selected from the group consisting of halogen, nitro, lower alkyl,

lower alkoxy, hydroxy, ar(lower)alkoxy and halo(lower)alkyl,

and

Y is -NHCO-.

4. A compound of claim 3, wherein

R^1 is lower alkyl; lower alkoxy(lower)alkyl; cyclo(lower)alkyl(lower)alkyl; halo(lower)alkyl; benzyl; pyridyl(lower)alkyl; lower alkenyl; cyclo(lower)alkyl; lower alkylamino; phenyl which may be substituted with a substituent selected from the group consisting of lower alkyl, halo(lower)alkyl, lower alkoxycarbonyl, nitro, amino and halogen; or pyridyl, quinolyl, isoxazolyl, thiazolyl, isothiazolyl or thiadiazolyl, each of which may be substituted with lower alkyl;

and

R^2 is hydrogen or lower alkyl,

or

R^1 and R^2 are taken together with the attached nitrogen atom to form morpholino, thiomorpholino, piperidino or 1-pyrrolidinyl,

and

R^7 is phenyl substituted with one or two halogen(s); phenyl substituted with nitro; phenyl substituted with halo(lower)alkyl; pyridyl substituted with one or two lower alkyl; pyridyl substituted with halo(lower)alkyl; pyridyl substituted with one or two halogen(s) and lower alkyl; or pyridyl substituted with one or two halogen(s).

5. A compound of claim 4, wherein

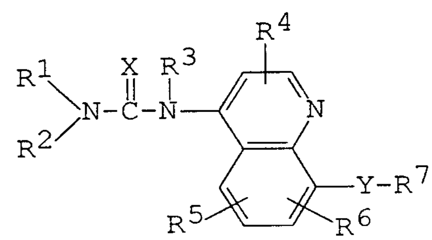
R^4 is hydrogen, lower alkyl or halogen,

R^5 and R^6 are each hydrogen,

and

R^7 is phenyl substituted with one or two halogen(s), phenyl substituted with halo(lower)alkyl, pyridyl substituted with one or two halogen(s) or pyridyl substituted with halo(lower)alkyl.

6. A process for preparing a compound of the formula :



wherein

R^1 is hydrogen; lower alkyl which may be substituted with substituent(s) selected from the group consisting of hydroxy, lower alkoxy, acyl, cyclo(lower)alkyl, halogen, aryl and a heterocyclic group;
lower alkenyl; cyclo(lower)alkyl;
amino; lower alkylamino;
substituted or unsubstituted aryl; or
substituted or unsubstituted heterocyclic group;
and

R^2 is hydrogen; or lower alkyl which may be substituted with a substituent selected from the group consisting of hydroxy and lower alkoxy;
or

R^1 and R^2 are taken together with the attached nitrogen atom to form substituted or unsubstituted N-containing heterocyclic-N-yl group,

R^3 is hydrogen or lower alkyl,

R^4 is hydrogen, halogen, cyano or lower alkyl which may be substituted with a substituent selected from the

group consisting of hydroxy and lower alkoxy,

R^5 and R^6 are each hydrogen, halogen, lower alkyl, lower alkoxy or halo(lower)alkyl,

R^7 is a heterocyclic group or aryl, each of which may be substituted with substituent(s) selected from the group consisting of halogen, nitro, lower alkyl, lower alkoxy, hydroxy, ar(lower)alkoxy and halo(lower)alkyl,

X is O or S,

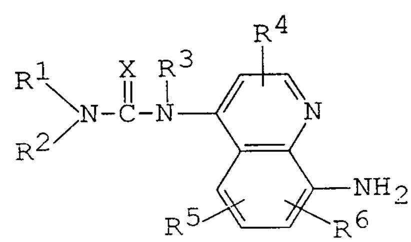
and

Y is -NHCO-, -CONH- or $-NH\overset{X^1}{\overset{\|}{C}}NH-$,

in which X^1 is O or S,

or its salt, which comprises

a) reacting a compound of the formula :



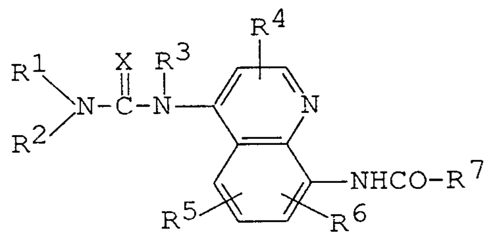
wherein R^1, R^2, R^3, R^4, R^5, R^6 and X are each as defined above,

or its reactive derivative at the amino group or a salt thereof with a compound of the formula :

$$R^7 - COOH$$

wherein R^7 is as defined above,

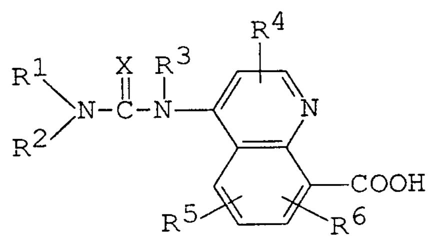
or its reactive derivative at the carboxy group or a salt thereof to give a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and X are each as defined above,

or its salt, or

b) reacting a compound of the formula :



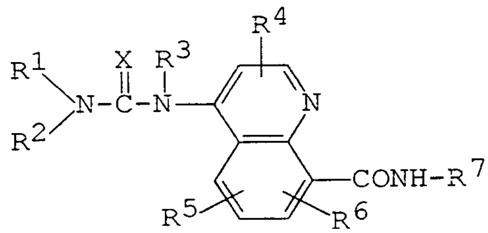
wherein R^1, R^2, R^3, R^4, R^5, R^6 and X are each as defined above,

or its reactive derivative at the carboxy group or a salt thereof with a compound of the formula :

$$R^7 - NH_2$$

wherein R^7 is as defined above,

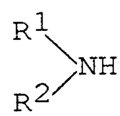
or its reactive derivative at the amino group or a salt thereof to give a compound of the formula :



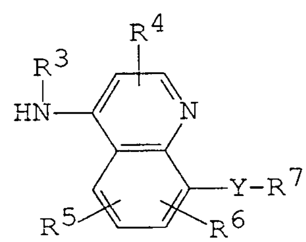
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and X are each as defined above,

or its salt, or

c) subjecting a compound of the formula :

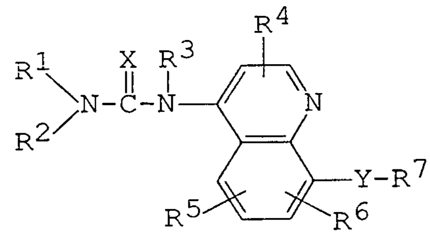


wherein R^1 and R^2 are each as defined above,
or its salt and a compound of the formula :



wherein R^3, R^4, R^5, R^6, R^7 and Y are each as defined above,

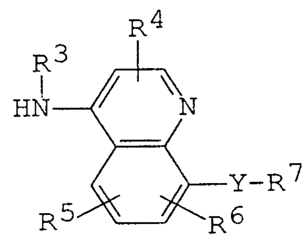
or its salt to a formation reaction of urea or thiourea group to give a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and Y are each as defined above,

or its salt, or

d) reacting a compound of the formula :



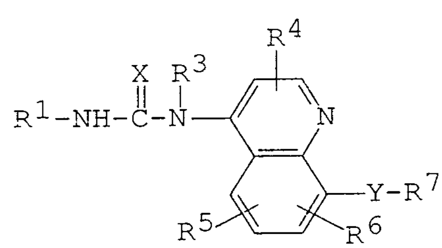
wherein R^3, R^4, R^5, R^6, R^7 and Y are each as defined above,

or its salt with a compound of the formula :

$$R^1 - NCX$$

wherein R^1 and X are each as defined above,

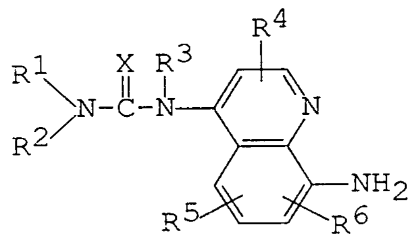
or its salt to give a compound of the formula :



wherein R^1, R^3, R^4, R^5, R^6, R^7, X and Y are each as defined above,

or its salt, or

e) reacting a compound of the formula :



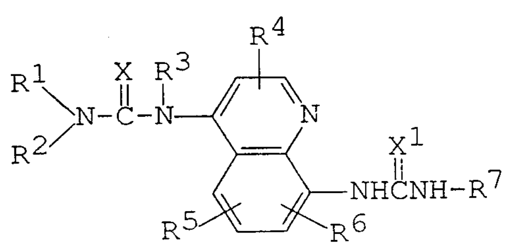
wherein R^1, R^2, R^3, R^4, R^5, R^6 and X are each as defined above,

or its salt with a compound of the formula :

$$R^7 - NCX^1$$

wherein R^7 and X^1 are each as defined above,

or its salt to give a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and X^1 are each as defined above,

or its salt.

7. A pharmaceutical composition comprising a compound of

claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially nontoxic carrier or excipient.

8. A compound of claim 1 for use as a medicament.

9. A method for the prevention and/or the treatment of bone diseases caused by abnormal bone metabolism which comprises administering a compound of claim 1 to human being or animals.

10. Use of a compound of claim 1 for manufacture of a medicament for the prevention and/or the treatment of bone diseases caused by abnormal bone metabolism.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/JP 98/04841

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D215/42 A61K31/47 C07D401/12 C07D417/12 C07D413/12
C07D215/12 C07D409/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 14681 A (FUJISAWA PHARMACEUTICAL CO.,LTD.) 24 April 1997 cited in the application see claims -----	1,7,8,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 January 1999	28/01/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 98/04841

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCi/JP 98/04841

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9714681 A	24-04-1997	AU 7228896 A	07-05-1997
		EP 0876345 A	11-11-1998